

DRWN No Drawings

LN.CNT 20253

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, **treating**, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 15 OF 221 USPATFULL

AN 2002:294651 USPATFULL

TI Methods and compositions for **treating** and preventing infection using human interferon regulatory factor 3

IN Moore, Paul A., Germantown, MD, UNITED STATES

Pith-Rowe, Paula, Baltimore, MD, UNITED STATES

PA Human Genome Sciences, Inc., Rockville, MD, UNITED STATES, 20850 (U.S. corporation)

PI US 2002164694 A1 20021107

AI US 2001-975253 A1 20011012 (9)

RLI Continuation-in-part of Ser. No. US 1996-705771, filed on 30 Aug 1996, GRANTED, Pat. No. US 6054289

PRAI US 2000-239936P 20001013 (60)

US 1995-2993P 19950830 (60)

DT Utility

FS APPLICATION

LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

CLMN Number of Claims: 36

ECL Exemplary Claim: 1

DRWN 4 Drawing Page(s)

LN.CNT 8370

AB The present invention relates to IRF3 polypeptides. In particular, isolated nucleic acid molecules are provided encoding human IRF3 protein. IRF3 polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods of gene therapy using polynucleotides encoding IRF3 polypeptides, fragments or variants to **treat**, prevent or ameliorate infectious diseases.

L9 ANSWER 16 OF 221 USPATFULL

AN 2002:294642 USPATFULL

TI Nucleic acids, proteins, and antibodies

IN Rosen, Craig A., Laytonsville, MD, UNITED STATES

Ruben, Steven M., Olney, MD, UNITED STATES

Barash, Steven C., Rockville, MD, UNITED STATES

PI US 2002164685 A1 20021107

AI US 2001-764857 A1 20010117 (9)

PRAI US 2000-179065P 20000131 (60)

US 2000-180628P 20000204 (60)

US 2000-214886P 20000628 (60)

US 2000-217487P 20000711 (60)

US 2000-225758P 20000814 (60)

US 2000-220963P 20000726 (60)

US 2000-217496P 20000711 (60)

US 2000-225447P	20000814 (60)
US 2000-218290P	20000714 (60)
US 2000-225757P	20000814 (60)
US 2000-226868P	20000822 (60)
US 2000-216647P	20000707 (60)
US 2000-225267P	20000814 (60)
US 2000-216880P	20000707 (60)
US 2000-225270P	20000814 (60)
US 2000-251869P	20001208 (60)
US 2000-235834P	20000927 (60)
US 2000-234274P	20000921 (60)
US 2000-234223P	20000921 (60)
US 2000-228924P	20000830 (60)
US 2000-224518P	20000814 (60)
US 2000-236369P	20000929 (60)
US 2000-224519P	20000814 (60)
US 2000-220964P	20000726 (60)
US 2000-241809P	20001020 (60)
US 2000-249299P	20001117 (60)
US 2000-236327P	20000929 (60)
US 2000-241785P	20001020 (60)
US 2000-244617P	20001101 (60)
US 2000-225268P	20000814 (60)
US 2000-236368P	20000929 (60)
US 2000-251856P	20001208 (60)
US 2000-251868P	20001208 (60)
US 2000-229344P	20000901 (60)
US 2000-234997P	20000925 (60)
US 2000-229343P	20000901 (60)
US 2000-229345P	20000901 (60)
US 2000-229287P	20000901 (60)
US 2000-229513P	20000905 (60)
US 2000-231413P	20000908 (60)
US 2000-229509P	20000905 (60)
US 2000-236367P	20000929 (60)
US 2000-237039P	20001002 (60)
US 2000-237038P	20001002 (60)
US 2000-236370P	20000929 (60)
US 2000-236802P	20001002 (60)
US 2000-237037P	20001002 (60)
US 2000-237040P	20001002 (60)
US 2000-240960P	20001020 (60)
US 2000-239935P	20001013 (60)

DT Utility

FS APPLICATION

LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 16891

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, **treating**, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 17 OF 221 USPATFULL  
AN 2002:291062 USPATFULL  
TI Secreted protein HNFGF20  
IN Komatsoulis, George, Silver Spring, MD, United States  
Rosen, Craig A., Laytonsville, MD, United States  
Ruben, Steven M., Olney, MD, United States  
Duan, Roxanne D., Bethesda, MD, United States  
Moore, Paul A., Germantown, MD, United States  
Shi, Yanggu, Gaithersburg, MD, United States  
LaFleur, David W., Washington, DC, United States  
Wei, Ying-Fei, Berkeley, CA, United States  
Ni, Jian, Rockville, MD, United States  
Florence, Kimberly A., Rockville, MD, United States  
Young, Paul, Gaithersburg, MD, United States  
Brewer, Laurie A., St. Paul, MN, United States  
Soppet, Daniel R., Centreville, VA, United States  
Endress, Gregory A., Potomac, MD, United States  
Ebner, Reinhard, Gaithersburg, MD, United States  
Olsen, Henrik, Gaithersburg, MD, United States  
Mucenski, Michael, Cincinnati, OH, United States  
PA Human Genome Sciences, Inc., Rockville, MD, United States (U.S.  
corporation)  
PI US 6476195 B1 20021105  
AI US 2000-489847 20000124 (9)  
RLI Continuation-in-part of Ser. No. WO 1999-US17130, filed on 29 Jul 1999  
PRAI US 1998-94657P 19980730 (60)  
US 1998-95486P 19980805 (60)  
US 1998-96319P 19980812 (60)  
US 1998-95454P 19980806 (60)  
US 1998-95455P 19980806 (60)  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Jones, W. Gary; Assistant Examiner: Goldberg, Jeanine  
LREP Human Genome Sciences, Inc.  
CLMN Number of Claims: 36  
ECL Exemplary Claim: 1,7  
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)  
LN.CNT 20107  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB The present invention relates to novel human secreted protein (HNFGF20).  
Polypeptides of the invention are useful in diagnosis and  
**treatment** of disorders affecting the immune system.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 18 OF 221 USPATFULL  
AN 2002:290742 USPATFULL  
TI 94 Human Secreted Proteins  
IN Ruben, Steven M., Olney, MD, United States  
Ni, Jian, Rockville, MD, United States  
Rosen, Craig A., Laytonsville, MD, United States  
Wei, Ying-Fei, Berkeley, CA, United States  
Young, Paul, Gaithersburg, MD, United States  
Florence, Kimberly, Rockville, MD, United States  
Soppet, Daniel R., Centreville, VA, United States  
Brewer, Laurie A., St. Paul, MN, United States  
Endress, Gregory A., Potomac, MD, United States  
Carter, Kenneth C., Potomac, MD, United States  
Mucenski, Michael, Cincinnati, OH, United States  
Ebner, Reinhard, Gaithersburg, MD, United States  
Lafleur, David W., Washington, DC, United States

Olsen, Henrik, Gaithersburg, MD, United States  
Shi, Yanggu, Gaithersburg, MD, United States  
Moore, Paul A., Germantown, MD, United States  
Komatsoulis, George, Silver Spring, MD, United States

PA Human Genome Sciences, Inc., Rockville, MD, United States (U.S.  
corporation)  
PI US 6475753 B1 20021105  
AI US 1999-461325 19991214 (9)  
RLI Continuation-in-part of Ser. No. WO 1999-US13418, filed on 15 Jun 1999  
PRAI US 1998-89507P 19980616 (60)  
US 1998-89508P 19980616 (60)  
US 1998-89509P 19980616 (60)  
US 1998-89510P 19980616 (60)  
US 1998-90112P 19980622 (60)  
US 1998-90113P 19980622 (60)  
DT Utility  
FS GRANTED  
EXNAM Primary Examiner: Eyler, Yvonne; Assistant Examiner: Hamud, Fozia  
LREP Human Genome Sciences, Inc.  
CLMN Number of Claims: 37  
ECL Exemplary Claim: 1  
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)  
LN.CNT 18031

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and **treating** disorders related to these novel human secreted proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 19 OF 221 USPATFULL  
AN 2002:288336 USPATFULL  
TI Nucleic acids, proteins, and antibodies  
IN Rosen, Craig A., Laytonsville, MD, UNITED STATES  
Ruben, Steven M., Olney, MD, UNITED STATES  
Barash, Steven C., Rockville, MD, UNITED STATES  
PI US 2002161208 A1 20021031  
AI US 2001-764884 A1 20010117 (9)  
PRAI US 2000-179065P 20000131 (60)  
DT Utility  
FS APPLICATION  
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850  
CLMN Number of Claims: 24  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 18396

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, **treating**, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.



CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 20 OF 221 USPATFULL  
AN 2002:288327 USPATFULL  
TI Compositions and methods for the diagnosis and **treatment** of  
tumor  
IN Ashkenazi, Avi, San Mateo, CA, UNITED STATES  
Goddard, Audrey, San Francisco, CA, UNITED STATES  
Godowski, Paul J., Burlingame, CA, UNITED STATES  
Gurney, Austin, Belmont, CA, UNITED STATES  
Polakis, Paul, Burlingame, CA, UNITED STATES  
Williams, P. Mickey, Half Moon Bay, CA, UNITED STATES  
Wood, William I., Hillsborough, CA, UNITED STATES  
Wu, Thomas D., San Francisco, CA, UNITED STATES  
Zhang, Zemin, Foster City, CA, UNITED STATES  
PA GENENTECH, INC. (U.S. corporation)  
PI US 2002161199 A1 20021031  
AI US 2001-938418 A1 20010823 (9)  
RLI Continuation of Ser. No. WO 1999-US5028, filed on 8 Mar 1999, UNKNOWN  
Continuation of Ser. No. WO 1999-US12252, filed on 2 Jun 1999, UNKNOWN  
Continuation of Ser. No. WO 1999-US20111, filed on 1 Sep 1999, UNKNOWN  
Continuation of Ser. No. WO 1999-US28565, filed on 2 Dec 1999, UNKNOWN  
Continuation of Ser. No. WO 2000-US4342, filed on 18 Feb 2000, UNKNOWN  
Continuation of Ser. No. WO 2000-US4341, filed on 18 Feb 2000, UNKNOWN  
Continuation of Ser. No. WO 2000-US5841, filed on 2 Mar 2000, UNKNOWN  
Continuation of Ser. No. WO 2000-US8439, filed on 30 Mar 2000, UNKNOWN  
Continuation of Ser. No. WO 2000-US14042, filed on 22 May 2000, UNKNOWN  
Continuation of Ser. No. WO 2000-US23328, filed on 24 Aug 2000, UNKNOWN  
Continuation of Ser. No. WO 2000-US32678, filed on 1 Dec 2000, UNKNOWN  
Continuation of Ser. No. WO 2001-US6520, filed on 28 Feb 2001, UNKNOWN  
Continuation of Ser. No. WO 2001-US17800, filed on 1 Jun 2001, UNKNOWN  
Continuation of Ser. No. WO 2001-US19692, filed on 20 Jun 2001, UNKNOWN  
Continuation of Ser. No. WO 2001-US21066, filed on 29 Jun 2001, UNKNOWN  
Continuation of Ser. No. WO 2001-US21735, filed on 9 Jul 2001, UNKNOWN  
PRAI US 1998-81071P 19980408 (60)  
US 1998-85697P 19980515 (60)  
US 1998-97022P 19980818 (60)  
US 1998-101922P 19980924 (60)  
US 1998-103679P 19981008 (60)  
DT Utility  
FS APPLICATION  
LREP Attn: Mark T. Kresnak, Ph.D., GENENTECH, INC., 1 DNA WAY, SOUTH SAN  
FRANCISCO, CA, 94000  
CLMN Number of Claims: 15  
ECL Exemplary Claim: 1  
DRWN 10 Drawing Page(s)  
LN.CNT 6560

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to compositions of matter useful for  
the diagnosis and **treatment** of tumor in mammals and to methods  
of using those compositions of matter for the same.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> file scisearch  
COST IN U.S. DOLLARS  
FULL ESTIMATED COST

SINCE FILE	TOTAL
ENTRY	SESSION
65.67	82.75

FILE 'SCISEARCH' ENTERED AT 10:35:53 ON 28 NOV 2002  
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FILE COVERS 1974 TO 26 Nov 2002 (20021126/ED)

=> s l4 and (gemcitabine or fluoropyrimidine or fluorouracil or cytidine)

3787 ANTHRACYCLINE  
2429 ANTHRACYCLINES  
5428 ANTHRACYCLINE  
(ANTHRACYCLINE OR ANTHRACYCLINES)  
3152 DAUNORUBICIN  
6 DAUNORUBICINS  
3155 DAUNORUBICIN  
(DAUNORUBICIN OR DAUNORUBICINS)  
14163 DOXORUBICIN  
11 DOXORUBICINS  
14168 DOXORUBICIN  
(DOXORUBICIN OR DOXORUBICINS)  
44013 SYNERG?  
2047 GEMCITABINE  
483 FLUOROPYRIMIDINE  
401 FLUOROPYRIMIDINES  
786 FLUOROPYRIMIDINE  
(FLUOROPYRIMIDINE OR FLUOROPYRIMIDINES)  
15257 FLUOROURACIL  
39 FLUOROURACILS  
15275 FLUOROURACIL  
(FLUOROURACIL OR FLUOROURACILS)  
3080 CYTIDINE  
91 CYTIDINES  
3139 CYTIDINE  
(CYTIDINE OR CYTIDINES)

L13 10 L4 AND (GEMCITABINE OR FLUOROPYRIMIDINE OR FLUOROURACIL OR CYTIDINE)

=> dis l13 1-10 bib abs

L13 ANSWER 1 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)

AN 2002:490830 SCISEARCH

GA The Genuine Article (R) Number: 559RQ

TI Future treatment options with capecitabine in solid tumours

AU Wilke H (Reprint)

CS Kliniken Essen Mitte, Dept Internal Med & Oncol Hematol, Essen, Germany (Reprint)

CYA Germany

SO EUROPEAN JOURNAL OF CANCER, (FEB 2002) Vol. 38, Supp. [2], pp. S21-S25.  
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE,  
KIDLINGTON, OXFORD OX5 1GB, ENGLAND.  
ISSN: 0959-8049.

DT Article; Journal

LA English

REC Reference Count: 27

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB The oral **fluoropyrimidine**, capecitabine is attracting great interest in the context of tumour-selective therapy and rationally designed combination regimens. Agents such as taxanes upregulate thymidine phosphorylase (TP), and there is therefore a clear rationale for their combination with capecitabine. Preclinical studies of capecitabine/taxane combination therapy demonstrated **synergistic** antitumour activity and phase I studies showed encouraging efficacy. Therefore, a randomised, phase III trial (docetaxel versus docetaxel/capecitabine) has been initiated in **anthracycline**-refractory metastatic breast cancer patients. Recruitment is complete. In colorectal cancer, capecitabine/oxaliplatin combination therapy is promising and a phase 1, dose-finding trial has been conducted in patients with refractory metastatic solid tumours. A similar trial has evaluated capecitabine/irinotecan combination treatment. Capecitabine is also being

investigated as adjuvant therapy for colorectal and breast cancers. The primary objective of the ongoing X-ACT trial in almost 2000 Dukes' C colon cancer patients is to demonstrate at least equivalent disease-free survival between capecitabine and the Mayo Clinic regimen. In addition, the CALGB is planning a randomised, phase III trial of capecitabine versus **doxorubicin**/cyclophosphamide or cyclophosphamide/methotrexate/5-fluorouracil (CMF) as adjuvant treatment in high-risk, node-negative breast cancer patients aged > 65 years. (C) 2002 Published by Elsevier Science Ltd.

L13 ANSWER 2 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)  
AN 2002:359575 SCISEARCH  
GA The Genuine Article (R) Number: 545BC  
TI **Doxorubicin** enhances TRAIL-induced apoptosis in prostate cancer  
AU Wu X X; Kakehi Y (Reprint); Mizutani Y; Kamoto T; Kinoshita H; Isogawa Y; Terachi T; Ogawa O  
CS Kagawa Med Univ, Dept Urol, Miki Cho, Kagawa 7610793, Japan (Reprint); Kagawa Med Univ, Dept Urol, Kagawa 7610793, Japan; Kyoto Univ, Grad Sch Med, Dept Urol, Kyoto 6068507, Japan; Kyoto Prefectural Univ Med, Dept Urol, Kyoto 6028566, Japan  
CYA Japan  
SO INTERNATIONAL JOURNAL OF ONCOLOGY, (MAY 2002) Vol. 20, No. 5, pp. 949-954. Publisher: PROFESSOR D A SPANDIDOS, 1, S MERKOURI ST, EDITORIAL OFFICE,, ATHENS 116 35, GREECE. ISSN: 1019-6439.  
DT Article; Journal  
LA English  
REC Reference Count: 34  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
AB Tumor necrosis factor-related apoptosis-inducing, ligand (TRAIL) induces apoptosis in various tumor cells. The **anthracycline doxorubicin** (DOX) can sensitize several types of cancer cells to TRAIL-mediated apoptosis. Here we report that DOX enhances TRAIL-induced apoptosis and cytotoxicity against prostate cancer cells. Cytotoxicity was determined by a MTT assay. **Synergistic** effect was assessed by isobolographic analysis. Caspase activity was determined by a quantitative colorimetric assay. The combination treatment with DOX and TRAIL resulted in a **synergistic** cytotoxic effect on LNCaP, LNCaP-Bcl-2, PC-3, and PC93 human prostate cancer cell lines, but not on normal human prostatic stromal cells. **Synergistic** cytotoxicity was also obtained even when the exposure time was shortened from 24 to 8 or 2 h. A similar effect was achieved with TRAIL in combination with epirubicin, pirarubicin, or amrubicin. The **synergy** obtained in cytotoxicity with TRAIL and DOX was also achieved in apoptosis. DOX treatment significantly activated caspase-8, 6, and -3 in LNCaP cells. Furthermore, the **synergistic** cytotoxicity of TRAIL and DOX was completely inhibited by Z-VAD-FMK, and partly inhibited by Ac-IETD-CHO, Ac-DQTD-CHO, or Ac-DMQD-CHO. These findings indicate that DOX enhances TRAIL-induced apoptosis and cytotoxicity in prostate cancer by activation of caspase cascades, and suggest that TRAIL in combination with DOX have a therapeutic potential in the treatment of prostate cancer.

L13 ANSWER 3 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)  
AN 2001:426479 SCISEARCH  
GA The Genuine Article (R) Number: 434HA  
TI In vitro induction of apoptosis of neoplastic cells in low-grade non-Hodgkin's lymphomas using combinations of established cytotoxic drugs with bendamustine  
AU Chow K U; Boehrer S; Geduldig K; Krapohl A; Hoelzer D; Mitrou P S; Weidmann E (Reprint)  
CS Univ Frankfurt, Dept Internal Med 3, Theodor Stern Kai 7, D-60590 Frankfurt, Germany (Reprint); Univ Frankfurt Klinikum, Dept Internal Med 3, D-6000 Frankfurt, Germany  
CYA Germany

SO HAEMATOLOGICA, (MAY 2001) Vol. 86, No. 5, pp. 485-493.  
 Publisher: FERRATA STORTI FOUNDATION, STRADA NUOVA 134, 27100 PAVIA,  
 ITALY.  
 ISSN: 0390-6078.

DT Article; Journal  
 LA English  
 REC Reference Count: 39  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Background and Objectives, Regulation of apoptotic cell death is being increasingly recognized as a mechanism by which cytostatic agents mediate tumor cell death. Preliminary clinical studies with bendamustine, an alkylating agent with a purine nucleus, provide strong evidence that this drug is a highly effective cytostatic in low grade lymphomas, We, therefore, investigated the in vitro activity of bendamustine in combination with other established cytotoxic drugs.

Design and Methods. Two cell lines (DOHH-2, WSU-NHL) and mononuclear cells (MNC) from patients with leukemic low-grade B-non-Hodgkin's lymphoma (NHL) (n=10), T-NHL (n=7) and chronic lymphocytic leukemia (CU) (n=12). Apoptosis (7-AAD), depolarization of mitochondrial membrane potential (MMP, JC-1), caspase-3-activity (FIENA) and cell proliferation (XTT/WST-1) were determined, Several incubation times and drug dosages (for IC30/50/70/90) were studied, **Synergistic**, additive or antagonistic effects were calculated by a median plot effect and the combination index (CI) method.

Results. In general, combinations of bendamustine with mitoxantrone or **doxorubicin** resulted in antagonistic effects in the tested cell lines and the MNC from the patients. CI-calculation failed in these cases since there was not a sufficient dose response. On the other hand, the combination of bendamustine with 2-CdA showed **synergistic** in vitro activity on the tested cell lines, neoplastic lymphocytes from patients with peripheral T-cell lymphomas and partially on MNC from patients with CU. and B-NHL The antagonism of the combination of bendamustine and **anthracyclines** appeared to be due to inhibition of depolarization of mitochondrial membrane potential and caspase-3-activity during apoptosis of the studied cell lines.

Interpretation and Conclusions. In conclusion, our results suggest that schedules using combinations of bendamustine and **anthracyclines** should not be recommended for the treatment of low-grade NHL whereas bendamustine combined with 2-CdA could be considered for the development of future treatment strategies. (C) 2001, Ferrata Storti Foundation.

L13 ANSWER 4 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)  
 AN 2000:751128 SCISEARCH  
 GA The Genuine Article (R) Number: 359GB  
 TI Induction of apoptosis using 2',2' difluorodeoxycytidine (**gemcitabine**) in combination with antimetabolites or **anthracyclines** on malignant lymphatic and myeloid cells. Antagonism or **synergism** depends on incubation schedule and origin of neoplastic cells

AU Chow K U; Ries J; Weidmann E; Pourebrahim F; Napieralski S; Stieler M; Boehrer S; Rummel M J; Stein J; Hoelzer D; Mitrou P S (Reprint)  
 CS UNIV FRANKFURT HOSP, DEPT INTERNAL MED 3, THEODOR STERN KAI 7, D-60590 FRANKFURT, GERMANY (Reprint); UNIV FRANKFURT HOSP, DEPT INTERNAL MED 3, D-60590 FRANKFURT, GERMANY; UNIV FRANKFURT HOSP, DEPT INTERNAL MED 2, D-60590 FRANKFURT, GERMANY  
 CYA GERMANY

SO ANNALS OF HEMATOLOGY, (SEP 2000) Vol. 79, No. 9, pp. 485-492. *date!*  
 Publisher: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.  
 ISSN: 0939-5555.

DT Article; Journal  
 FS LIFE; CLIN  
 LA English  
 REC Reference Count: 34  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Induction of apoptosis in vitro using **gemcitabine** (dFdC) in combination with cladribine (2-CdA) and other cytotoxic drugs on malignant mononuclear cells (MNCs) of patients with acute myeloid leukemia (AML, n = 20) and chronic lymphocytic leukemia (CLL, n = 20) in myeloid (HL60, HEL) and lymphatic cell lines (HUT78, JURKAT) was investigated using different incubation conditions (simultaneous and consecutive). Furthermore, the influence of dFdC on the level of intracellular metabolites of 2-CdA was studied using high-performance liquid chromatography (HPLC). Apoptosis was evaluated using flow cytometry with 7-aminoactinomycin D. In MNCs of patients with CLL, dFdC + 2-CdA showed an antagonistic effect when applied simultaneously. This antagonism was reduced by consecutive application. The combination of dFdC with **doxorubicin** was **synergistic**, independent of incubation schedule. In blasts from newly diagnosed patients with de novo AML, all drug combinations (dFdC + 2-CdA, **doxorubicin**, or cytosine arabinoside) were antagonistic by simultaneous incubation. Reduced antagonism or even **synergism** was shown ( $P < 0.001$ ) by consecutive incubation. The simultaneous combination of dFdC with 2-CdA in all tested cell lines resulted in a competitive inhibition on the rate of apoptosis. By changing the incubation period to a consecutive schedule, the antagonism was diminished or **synergism** of apoptosis was measured ( $P < 0.001$ ). Using similar incubation conditions, these experiments were supported by HPLC measurement of intracellular metabolites of 2-CdA influenced by dFdC application. In conclusion, we demonstrated that the efficacy of dFdC in vitro in combination with other cytotoxic drugs depends on the incubation condition and on the origin of neoplastic cells (lymphatic vs myeloid). The data suggest that simultaneous combination therapy with purine and pyrimidine analogues may not improve the clinical efficacy of one or the other drug administered alone. *date not specified*

L13 ANSWER 5 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)  
AN 1999:273906 SCISEARCH  
GA The Genuine Article (R) Number: 182YE  
TI Inhibitory effects of combinations of HER-2/neu antibody and  
chemotherapeutic agents used for treatment of human breast cancers  
AU Pegram M; Hsu S; Lewis G; Pietras R; Beryt M; Sliwkowski M; Coombs D; Baly  
D; Kabbinavar F; Slamon D (Reprint)  
CS UNIV CALIF LOS ANGELES, SCH MED, DEPT MED, DIV HEMATOL ONCOL, 11-934  
FACTOR BLDG, LOS ANGELES, CA 90095 (Reprint); UNIV CALIF LOS ANGELES, SCH  
MED, DEPT MED, DIV HEMATOL ONCOL, LOS ANGELES, CA 90095; GENENTECH INC,  
SAN FRANCISCO, CA 94080  
CYA USA  
SO ONCOGENE, (1 APR 1999) Vol. 18, No. 13, pp. 2241-2251.  
Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE,  
ENGLAND.  
ISSN: 0950-9232.  
DT Article; Journal  
FS LIFE  
LA English  
REC Reference Count: 47  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
AB Previous studies have demonstrated a **synergistic** interaction  
between rhuMab HER2 and the cytotoxic drug cisplatin in human breast and  
ovarian cancer cells. To define the nature of the interaction between  
rhuMab HER2 and other classes of cytotoxic drugs, we applied multiple drug  
effect/combination index (CI) isobologram analysis to a variety of  
chemotherapeutic drug/rhuMab HER2 combinations in vitro.  
**Synergistic** interactions at clinically relevant drug  
concentrations were observed for rhuMab HER2 in combination with cisplatin  
(CI = 0.48,  $P = 0.003$ ), thiotepa (CI = 0.67,  $P = 0.0008$ ), and etoposide  
(CI = 0.54,  $P = 0.0003$ ). Additive cytotoxic effects were observed with  
rhuMab HER2 plus **doxorubicin** (CI = 1.16,  $P = 0.13$ ), paclitaxel  
(CI = 0.91,  $P = 0.21$ ), methotrexate (CI = 1.15,  $P = 0.28$ ), and vinblastine  
(CI = 1.09,  $P = 0.26$ ). One drug, 5-fluorouracil, was found to be

antagonistic with rhuMab HER2 in vitro (CI = 2.87, P = 0.0001). In vivo drug/rhuMab HER2 studies were conducted with HER-2/neu-transfected, MCF7 human breast cancer xenografts in athymic mice. Combinations of rhuMab HER2 plus cyclophosphamide, **doxorubicin**, paclitaxel, methotrexate, etoposide, and vinblastine in vivo resulted in a significant reduction in xenograft volume compared to chemotherapy alone (P < 0.05). Xenografts treated with rhuMab HER2 plus 5-**fluorouracil** were not significantly different from 5-**fluorouracil** alone controls consistent with the subadditive effects observed with this combination in vitro. The **synergistic** interaction of rhuMab HER2 with alkylating agents, platinum analogs and topoisomerase II inhibitors, as well as the additive interaction with taxanes, **anthracyclines** and some antimetabolites in HER-2/neu-overexpressing breast cancer cells demonstrates that these are rational combinations to test in human clinical trials.

L13 ANSWER 6 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)  
 AN 1998:594896 SCISEARCH  
 GA The Genuine Article (R) Number: 104VP  
 TI Enhancement of chemotherapeutic drug toxicity to human tumour cells in vitro by a subset of non-steroidal anti-inflammatory drugs (NSAIDs)  
 AU Duffy C P; Elliott C J; OConnor R A; Heenan M M; Coyle S; Cleary I M; Kavanagh K; Verhaegen S; O'Loughlin C M; NicAmhlaoibh R; Clynes M (Reprint)  
 CS DUBLIN CITY UNIV, NATL CELL & TISSUE CULTURE CTR, DUBLIN 9, IRELAND (Reprint); DUBLIN CITY UNIV, NATL CELL & TISSUE CULTURE CTR, DUBLIN 9, IRELAND  
 CYA IRELAND  
 SO EUROPEAN JOURNAL OF CANCER, (JUL 1998) Vol. 34, No. 8, pp. 1250-1259. Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND. ISSN: 0959-8049.  
 DT Article; Journal  
 FS LIFE; CLIN  
 LA English  
 REC Reference Count: 50  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
 AB The effect on cytotoxicity of combining a range of clinically important non-steroidal anti-inflammatory drugs (NSAIDs) with a variety of chemotherapeutic drugs was examined in the human lung cancer cell Lines DLKP, A549, COR L23P and COR L23R and in a human leukaemia line HL60/ADR. A specific group of NSAIDs (indomethacin, sulindac, tolmetin, acemetacin, zomepirac and mefenamic acid) all at non-toxic levels, significantly increased the cytotoxicity of the **anthracyclines** (**doxorubicin**, **daunorubicin** and **epirubicin**), as well as teniposide, VP-16 and vincristine, but not the other vinca alkaloids vinblastine and vinorelbine. A substantial number of other anticancer drugs, including methotrexate, 5-**fluorouracil**, cytarabine, hydroxyurea, chlorambucil, cyclophosphamide, cisplatin, carboplatin, mitoxantrone, actinomycin D, bleomycin, paclitaxel and camptothecin, were also tested, but displayed no **synergy** in combination with the NSAIDs. The **synergistic** effect was concentration dependent. The effect appears to be independent of the cyclo-oxygenase inhibitory ability of the NSAIDs, as (i) the **synergistic** combination could not be reversed by the addition of prostaglandins D-2 or E-2; (ii) sulindac sulphone, a metabolite of sulindac that does not inhibit the cyclooxygenase enzyme, was positive in the combination assay: and (iii) many NSAIDs known to be cyclo-oxygenase inhibitors, e.g. meclofenamic acid, diclofenac, naproxen, fenoprofen, phenylbutazone, flufenamic acid, flurbiprofen, ibuprofen and ketoprofen, were inactive in the combination assay. The enhancement of cytotoxicity was observed in a range of drug sensitive tumour cell lines, but did not occur in P-170-overexpressing multidrug resistant cell lines. However, in the HL60/ADR and COR L23R cell lines, in which multidrug resistance is due to overexpression of the multidrug resistance-associated protein MRP, a significant increase in

cytotoxicity was observed in the presence of the active NSAIDs. Subsequent Western blot analysis of the drug sensitive parental cell lines, DLKP and A549, revealed that they also expressed MRP and reverse-transcription-polymerase chain reaction studies demonstrated that mRNA for MRP was present in both cell lines. It was found that the positive NSAIDs were among the more potent inhibitors of [H-3]-LTC<sub>4</sub> transport into inside-out plasma membrane vesicles prepared from MRP-expressing cells, of **doxorubicin** efflux from preloaded cells and of glutathione-S-transferase activity. The NSAIDs did not enhance cellular sensitivity to radiation. The combination of specific NSAIDs with anticancer drugs reported here may have potential clinical applications, especially in the circumvention of MRP-mediated multidrug resistance. (C) 1998 Elsevier Science Ltd. All rights reserved.

L13 ANSWER 7 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)  
 AN 1998:421036 SCISEARCH  
 GA The Genuine Article (R) Number: ZQ104  
 TI Combination of cisplatin-procaine complex DPR with anticancer drugs increases cytotoxicity against ovarian cancer cell lines  
 AU Viale M (Reprint); Pastrone I; Pellicchia C; Vannozzi M O; Cafaggi S; Esposito M  
 CS IST NAZL RIC CANC, SERV FARMACOL TOSSICOL, L O R BENZI 10, I-16132 GENOA, ITALY (Reprint); UNIV GENOA, IST ANAL & TECNOL FARMACEUT, I-16148 GENOA, ITALY  
 CYA ITALY  
 SO ANTI-CANCER DRUGS, (FEB 1998) Vol. 9, No. 5, pp. 457-463.  
 Publisher: RAPID SCIENCE PUBLISHERS, 2-6 BOUNDARY ROW, LONDON SE1 8NH, ENGLAND.  
 ISSN: 0959-4973.  
 DT Article; Journal  
 FS LIFE; CLIN  
 LA English  
 REC Reference Count: 12  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
 AB DPR, cis-diamminechloro-[2-(diethylamino)ethyl 4-aminobenzoate, N<sub>4</sub>]-chlorideplatinum(II) monohydrochloride monohydrate, is a newly developed water-soluble platinum compound which possesses minimal cross-resistance to cisplatin and shows relatively less side effects. In an attempt to establish whether the combination of DPR with other conventional anticancer drugs would be of any benefit we assessed in vitro the cytotoxic effects of combinations of DPR with the antimetabolites 5-**fluorouracil** (5-FU) and methotrexate (MTX), the alkylating agents mitomycin C (MMC) and cisplatin, the antimicrotubule agent taxol (TAX), and the intercalating agent of the **anthracycline** group **doxorubicin** (DOX) on murine M5076 ovarian reticulosarcoma and human A2780 ovarian carcinoma cells. These agents were selected because of their common use in the clinic and because they represent four distinct categories of antineoplastic mechanisms. Cells were incubated for 72 h in the presence of single or combined drugs, and the cytotoxic effect was determined by the MTT assay. The analysis of combination treatment was made by the isobole method. In human A2780 cells, an overall **synergy** was found for DPR combined with 5-FU, DOX and cisplatin. **Synergistic** effects were also observed for most combinations with MTX or MMC. A DPR concentration-dependent additivity and antagonism was seen at the highest MTX concentration (1  $\mu$  M), while additive effects were observed for the combined treatments of DPR and low concentrations of MMC (0.008 and 0.0016  $\mu$  M). Additive effects were also observed for the association of DPR and TAX over most combinations tested. In murine M5076 cells, **synergism** was the prevailing result observed when DPR was combined with 5-FU, DOX, MMC or cisplatin. When administered together with MTX we observed additivity over most combinations tested. These findings suggest that DPR, when simultaneously administered with standard anticancer agents, may be advantageous for cytotoxicity. [(C) 1998 Lippincott-Raven Publishers.]

L13 ANSWER 8 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)  
 AN 1998:312021 SCISEARCH  
 GA The Genuine Article (R) Number: ZH248  
 TI New developments in cancer treatment with the novel thymidylate synthase inhibitor raltitrexed ('Tomudex')  
 AU Blackledge G (Reprint)  
 CS ZENECA PHARMACEUT, CLIN RES GRP, ALDERLEY PK, MACCLESFIELD SK10 4TG, CHESHIRE, ENGLAND (Reprint)  
 CYA ENGLAND  
 SO BRITISH JOURNAL OF CANCER, (23 FEB 1998) Vol. 77, Supp. [2], pp. 29-37. Publisher: CHURCHILL LIVINGSTONE, JOURNAL PRODUCTION DEPT, ROBERT STEVENSON HOUSE, 1-3 BAXTERS PLACE, LEITH WALK, EDINBURGH EH1 3AF, MIDLOTHIAN, SCOTLAND. ISSN: 0007-0920.  
 DT Article; Journal  
 FS LIFE; CLIN  
 LA English  
 REC Reference Count: 46  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
 AB Following the demonstration of efficacy, tolerability and quality-of-life benefits of raltitrexed ('Tomudex'), principally in advanced colorectal but also in other cancers, an extensive evaluation of combination therapy with other agents in patients with colorectal and other tumour types is being undertaken. This work has been prompted by preclinical observations of enhanced activity of raltitrexed when coadministered with other cytotoxic agents or radiotherapy and by preliminary results showing the activity of raltitrexed in patients with cancers other than colorectal. Raltitrexed is currently being investigated as monotherapy in phase I and II cancer studies, including head and neck cancer, hormone-resistant prostate cancer, paediatric and adult leukaemias and solid tumours, and soft tissue sarcoma. In addition, phase I clinical trials are evaluating the drug in combination with taxanes (paclitaxel) in solid tumours, **anthracyclines** (doxorubicin) in gastric carcinoma, topoisomerase I inhibitors (CPT-11) and 5-**fluorouracil** (both infusion and bolus regimens) in advanced colorectal cancer, platinum compounds (oxaliplatin and cisplatin) in a variety of tumours and radiotherapy in rectal cancer. Preliminary reports indicate good tolerability and acceptability of the combinations being investigated, with no dose-limiting toxicity being reported to date, and some early indications of efficacy.

L13 ANSWER 9 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)  
 AN 94:213273 SCISEARCH  
 GA The Genuine Article (R) Number: NE269  
 TI CYCLOPHOSPHAMIDE, MITOXANTRONE AND **FLUOROURACIL** VERSUS CYCLOPHOSPHAMIDE, MITOXANTRONE AND **FLUOROURACIL** PLUS LONIDAMINE FOR THE TREATMENT OF ADVANCED BREAST-CANCER - A MULTICENTRIC RANDOMIZED CLINICAL-TRIAL  
 AU LORUSSO V; CATINO A; BRANDI M; PIANO A; PALOMBA G; FORCIGNANO R; MAZZOTTA S; MUSCA F; SERRAVEZZA G; DURINI E; CONTILLO A; PEZZELLA G; PALAZZO S; CHETRI C; DELENA M (Reprint)  
 CS ONCOL INST, VIA AMENDOLA 209, I-70126 BARI, ITALY (Reprint); ONCOL INST, I-70126 BARI, ITALY; OSPED DI SUMMA, BRINDISI, ITALY; CTR ONCOL, COSENZA, ITALY; OSPED SS ANNUNZIATA, TARANTO, ITALY; OSPED RIUNITI FOGGIA, FOGGIA, ITALY; OSPED F PANICO, TRICASE, ITALY; OSPED CIVILE, CASARANO, ITALY; OSPED CIVILE, POGGIARDO, ITALY; OSPED V FAZZI, CTR ONCOL, LECCE, ITALY; CASA SOLLIEVO SOFFERENZA, SAN GIOVANNI ROTONDO, ITALY  
 CYA ITALY  
 SO INTERNATIONAL JOURNAL OF ONCOLOGY, (MAR 1994) Vol. 4, Supp. S, pp. 767-772. ISSN: 1019-6439.  
 DT Article; Journal  
 FS LIFE



LA ENGLISH

REC Reference Count: 19

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Lonidamine (LND), a non conventional antineoplastic drug, is a biomodulating agent demonstrating a **synergistic** effect with cytotoxic drugs such as alkylating agents and **anthracyclines**. From July 1990 to May 1993, 206 patients with advanced breast cancer were studied to verify if LND plus CNF (cyclophosphamide, novantrone, **fluorouracil**) was able to enhance CNF activity with regard to response rate, time to progression and survival. After stratification, patients were randomized to receive CNF alone (group A) or CNF plus LND (450 mg orally 3 times a day) (group B). After 8 cycles, patients showing complete or partial response stopped treatment, and patients of group B continued to receive LND alone until disease progression. Overall response rate was 48% in group B versus 39% in group A (p=0.26). Although this difference was not statistically significant, more complete responses (CR) were observed in the LND treated group, especially in patients with soft tissue lesions, (CR rate: 47% versus 21%, respectively) and time to progression was significantly longer, suggesting that LND is able to prolong response duration. Conversely, no differences were observed with regard to overall survival.

L13 ANSWER 10 OF 10 SCISEARCH COPYRIGHT 2002 ISI (R)

AN 94:213272 SCISEARCH

GA The Genuine Article (R) Number: NE269

TI FEC (**FLUOROURACIL**, EPIRUBICIN AND CYCLOPHOSPHAMIDE) VERSUS EM (EPIRUBICIN AND MITOMYCIN-C) WITH OR WITHOUT LONIDAMINE AS FIRST LINE TREATMENT FOR ADVANCE BREAST-CANCER - A MULTICENTRIC RANDOMIZED STUDY - PRELIMINARY-REPORT

AU PACINI P (Reprint); ALGERI R; RINALDINI M; GUARNIERI A; BASTIANI P; BARSANTI G; NERI B; MARZANO S; TUCCI E

CS POLICLIN CAREGGI, DEPT RADIAT & MED ONCOL, VIALE MORGAGNI, I-50134 FLORENCE, ITALY (Reprint); OSPED CIVILE, GROSSETO, ITALY; OSPED CIVILE, CTR ONCOL, AREZZO, ITALY; POLICLIN LE SCOTTE, IST SCI CHIRURG, SIENA, ITALY; POLICLIN CAREGGI, DAY HOSP ONCOL, IST CLIN MED 4, FLORENCE, ITALY; POLICLIN SIENA, DAY HOSP ONCOL, DIV RADIOTERAPIA ONCOL, SIENA, ITALY; POLICLIN CAREGGI, DAY HOSP ONCOL, DIV RADIOTERAPIA ONCOL, FLORENCE, ITALY; OSPED CIVILE, DAY HOSP ONCOL, DIV RADIOTERAPIA, LIVORNO, ITALY; OSPED CAMPO MARTE, DAY HOSP ONCOL, DIV MED 1, LUCCA, ITALY

CYA ITALY

SO INTERNATIONAL JOURNAL OF ONCOLOGY, (MAR 1994) Vol. 4, Supp. S, pp. 761-766.

ISSN: 1019-6439.

DT Article; Journal

FS LIFE

LA ENGLISH

REC Reference Count: 25

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB In experimental models, both in vivo and in vitro, and in clinical studies, lonidamine demonstrated a **synergistic** activity with **anthracyclines** and increased their cytotoxicity. In a randomized clinical trial two different epirubicin containing regimens (epirubicin (E), 75 mg/m<sup>2</sup> every three weeks and mitomycin-C (M), 10 mg/m<sup>2</sup> every six weeks. FEC: **fluorouracil** 500 mg/m<sup>2</sup>, epirubicin 75 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> every three weeks) were compared with or without the addition of lonidamine (L) as first line treatment for patients with advanced breast cancer. Lonidamine was given orally at a dosage of 600 mg/day. Patients were randomly allocated to receive FEC, EM, FECL or EML. A factorial two by two design was followed to analyze the results (FEC/FECL versus EM/EML and FEC/EM versus FECL/EML). EM regimen showed a higher activity than FEC (CR+PR: EM/EML 76.4%, FEC/FECL 60%). A higher response rate was observed in the patients receiving lonidamine with respect to those not receiving this drug (CR+PR: FECL/EML 76.2%, FEC/EM 61.4%). Median time to progression was longer in the group

submitted to EM chemotherapy (EM/EML: 302 days, FEC/FECL: 237 days) and in the patients receiving lonidamine (FECL/EML: 320 days, FEC/EM: 266 days). These preliminary results suggest that EM combination is highly active against breast cancer and that the addition of lonidamine to **anthracycline** containing regimens can increase their activity.

=> FIL STNGUIDE  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
46.84	129.59

FULL ESTIMATED COST

FILE 'STNGUIDE' ENTERED AT 10:36:55 ON 28 NOV 2002  
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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.  
LAST RELOADED: Nov 22, 2002 (20021122/UP).

=>

---Logging off of STN---

=>  
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.06	129.65

FULL ESTIMATED COST

STN INTERNATIONAL LOGOFF AT 10:37:25 ON 28 NOV 2002

L Number	Hits	Search Text	DB	Time stamp
1	2981	anthracycline	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 16:59
2	117	anthracycline and gemcitabine	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:00
3	26	(anthracycline and gemcitabine) and synerg\$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:00
4	26	((anthracycline and gemcitabine) and synerg\$) and tumor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:02
5	1247	anthracycline and daunorubicin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:02
6	109	(anthracycline and daunorubicin) and gemcitabine	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:02
7	24	((anthracycline and daunorubicin) and gemcitabine) and synerg\$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:06
8	598	(anthracycline and daunorubicin) and 5-fluorouracil	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:07
9	172	((anthracycline and daunorubicin) and 5-fluorouracil) and synerg\$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:07
10	172	((anthracycline and daunorubicin) and 5-fluorouracil) and synerg\$) and tumor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:13
11	1561	anthracycline and doxorubicin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:14
12	702	(anthracycline and doxorubicin) and (gemcitabine or 5-fluorouracil or 5-fluoropyrimidine)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:15
13	201	((anthracycline and doxorubicin) and (gemcitabine or 5-fluorouracil or 5-fluoropyrimidine)) and synerg\$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:15
14	201	((anthracycline and doxorubicin) and (gemcitabine or 5-fluorouracil or 5-fluoropyrimidine)) and synerg\$) and tumor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:16
15	200	((anthracycline and doxorubicin) and (gemcitabine or 5-fluorouracil or 5-fluoropyrimidine)) and synerg\$) and tumor) and method	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:16
16	197	((anthracycline and doxorubicin) and (gemcitabine or 5-fluorouracil or 5-fluoropyrimidine)) and synerg\$) and tumor) and method) and (combination and therapy)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:34
17	407	anthracycline and synerg\$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:35

18	249	(anthracycline and synerg\$) and (gemcitabine or cytidine or fluorouracil or fluoropyrimide)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:35
19	245	((anthracycline and synerg\$) and (gemcitabine or cytidine or fluorouracil or fluoropyrimide)) and (cancer or tumor or neoplastic)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:36
20	244	((anthracycline and synerg\$) and (gemcitabine or cytidine or fluorouracil or fluoropyrimide)) and (cancer or tumor or neoplastic)) and method	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 17:36

L Number	Hits	Search Text	DB	Time stamp
1	2981	anthracycline	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 10:43
2	1247	anthracycline and daunorubicin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 10:43
3	1155	(anthracycline and daunorubicin) and (cancer or tumor or antineoplastic)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 10:44
4	234	((anthracycline and daunorubicin) and (cancer or tumor or antineoplastic)) and synergis	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 10:44
5	256	((anthracycline and daunorubicin) and (cancer or tumor or antineoplastic)) and synergis	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 10:44
6	144	((anthracycline and daunorubicin) and (cancer or tumor or antineoplastic)) and synergis) and antimetabolite	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 10:45
7	135	((anthracycline and daunorubicin) and (cancer or tumor or antineoplastic)) and synergis) and antimetabolite) and (gemcitabine or fluorouracil or fluoropyrimidine)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 10:46
8	135	((anthracycline and daunorubicin) and (cancer or tumor or antineoplastic)) and synergis) and antimetabolite) and (gemcitabine or fluorouracil or fluoropyrimidine)) and (method or treatment or composition or angiogenesis)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/27 10:47

L Number	Hits	Search Text	DB	Time stamp
1	3315	daunorubicin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:21
2	779	daunorubicin and synerg\$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:21
3	619	((daunorubicin and synerg\$) and (fluoropyrididine or fluorouracil or gemcitabine or cytidine))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:22
4	612	((daunorubicin and synerg\$) and (fluoropyrididine or fluorouracil or gemcitabine or cytidine)) and (cancer or tumor or neoplastic or angiogenesis or metastasis)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:23
5	609	((daunorubicin and synerg\$) and (fluoropyrididine or fluorouracil or gemcitabine or cytidine)) and (cancer or tumor or neoplastic or angiogenesis or metastasis)) and (method or process and treatment)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:24
6	2	((daunorubicin and synerg\$) and (fluoropyrididine or fluorouracil or gemcitabine or cytidine)) and (cancer or tumor or neoplastic or angiogenesis or metastasis)) and (method or process and treatment)) and 5-fluoro	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:27
7	235	((daunorubicin and synerg\$) and (fluoropyrididine or fluorouracil or gemcitabine or cytidine)) and antimetabolite	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:27
8	231	((daunorubicin and synerg\$) and (fluoropyrididine or fluorouracil or gemcitabine or cytidine)) and antimetabolite) and (cancer or tumor or neoplastic)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:28
9	2	((daunorubicin and synerg\$) and (fluoropyrididine or fluorouracil or gemcitabine or cytidine)) and antimetabolite) and (cancer or tumor or neoplastic)) and 5-fluoro	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:28
10	230	((daunorubicin and synerg\$) and (fluoropyrididine or fluorouracil or gemcitabine or cytidine)) and antimetabolite) and (cancer or tumor or neoplastic)) and (method or process and treatment)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:32
11	532	(daunorubicin and synerg\$) and 5-fluorouracil	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:32
12	530	((daunorubicin and synerg\$) and 5-fluorouracil) and cancer	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:33
13	529	((daunorubicin and synerg\$) and 5-fluorouracil) and cancer) and treat\$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:34
14	473	536/6.4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:34
16	11	(536/6.4 and synerg\$) and (5-fluorouracil or 5-fluoropyrimidine)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:35

15	27	536/6.4 and synerg\$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/29 08:36
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L7 ANSWER 12 OF 18 MEDLINE  
 AN 97223915 MEDLINE  
 DN 97223915 PubMed ID: 9070496  
 TI **Doxorubicin** sensitizes human bladder carcinoma cells to Fas-mediated cytotoxicity.  
 AU Mizutani Y; Okada Y; Yoshida O; Fukumoto M; Bonavida B  
 CS Department of Urology, Faculty of Medicine, Kyoto University, Japan.  
 SO CANCER, (1997 Mar 15) 79 (6) 1180-9.  
 Journal code: 0374236. ISSN: 0008-543X.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals  
 EM 199704  
 ED Entered STN: 19970424  
 Last Updated on STN: 19970424  
 Entered Medline: 19970415  
 AB BACKGROUND: The resistance of bladder carcinoma to anticancer chemotherapeutic agents remains a major problem. Hence, several immunotherapeutic approaches have been developed to treat the drug-resistant cancer cells. Fas antigen (Fas) and Fas ligand participate in cytotoxicity mediated by T lymphocytes and natural killer cells. Like Fas ligand, anti-Fas monoclonal antibody (MoAb) induces apoptosis of the cells expressing Fas. This study examined whether bladder carcinoma cells are sensitive to cytotoxicity mediated by anti-Fas MoAb and whether anticancer agents **synergize** with anti-Fas MoAb in cytotoxicity. METHODS: Cytotoxicity was determined by a 1-day microculture tetrazolium dye assay. **Synergy** was assessed by isobolographic analysis. RESULTS: The T24 human bladder carcinoma cell line constitutively expressed the Fas on the cell surface; however, T24 line was resistant to anti-Fas MoAb. Treatment of T24 cells with anti-Fas MoAb in combination with mitomycin C, methotrexate, or 5-**fluorouracil** did not overcome their resistance to these agents. However, treatment of T24 cells with a combination of anti-Fas MoAb and **doxorubicin** resulted in a **synergistic** cytotoxic effect. In addition, the **doxorubicin**-resistant T24 cells were sensitive to treatment with a combination of anti-Fas MoAb and **doxorubicin**. **Synergy** was also achieved in three other bladder carcinoma cell lines and four freshly derived human bladder carcinoma cells. Treatment with anti-Fas MoAb in combination with epirubicin or pirarubicin also resulted in a **synergistic** cytotoxic effect on T24 cells. The mechanisms of **synergy** were examined. Anti-Fas MoAb did not affect the intracellular accumulation of **doxorubicin**, the expression of P-glycoprotein, or the expression of the antioxidant glutathione S-transferase-pi mRNA. However, treatment with **doxorubicin** enhanced the expression of Fas on T24 cells. CONCLUSIONS: This study demonstrated that treatment of bladder carcinoma cells with **doxorubicin** sensitized the cells to lysis by anti-Fas MoAb. The **synergistic** effect obtained with established **doxorubicin**-resistant bladder carcinoma cells and freshly isolated bladder carcinoma cells suggests that drug-resistant bladder carcinoma cells can be sensitized by **doxorubicin** to Fas- and Fas ligand-mediated cytotoxicity by lymphocytes. Furthermore, the sensitization required low concentrations of **doxorubicin**, thus supporting the in vivo application of a combination of chemotherapy and immunotherapy in the treatment of drug-resistant and/or immunotherapy-resistant bladder carcinoma.

L7 ANSWER 13 OF 18 MEDLINE  
 AN 97205972 MEDLINE  
 DN 97205972 PubMed ID: 9157070  
 TI Effects of 13-hydroxy SM5887 in combination with other anticancer agents on human tumor cell lines.  
 AU Takagi T; Yazawa Y; Suzuki K; Yamauchi Y; Kano Y



CS Division of Orthopedic Oncology, Tochigi Cancer Center, Japan.  
 SO INVESTIGATIONAL NEW DRUGS, (1996) 14 (4) 357-63.  
 Journal code: 8309330. ISSN: 0167-6997.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199705  
 ED Entered STN: 19970602  
 Last Updated on STN: 19970602  
 Entered Medline: 19970520  
 AB A new **anthracycline** derivative, SM5887, in combination with commonly used anticancer agents was evaluated against T-cell leukemia MOLT-3 and human osteosarcoma MG-63 cell lines in culture. MOLT-3 and MG-63 cells were incubated with various concentrations of 13-hydroxy SM5887 (SM5887-OH, the active metabolite of SM5887) and other drugs for 3 and 4 days, respectively. Cell growth inhibition was determined by MTT assay. The antitumor effects of the drug combinations at 80% inhibitory concentration (IC80) were analyzed by the isobologram of Steel and Peckham. In MOLT-3 cells, SM5887-OH had additive effects with bleomycin, etoposide, **doxorubicin**, cisplatin, mitomycin-C, 4-hydroperoxy ifosfamide, 5-**fluorouracil**, cytarabine, and vincristine, whereas it had mainly protective (marked antagonistic) effects with methotrexate. In MG-63 cells, SM5887-OH had additive effects with bleomycin, etoposide, **doxorubicin**, cisplatin, mitomycin-C, 4-hydroperoxy ifosfamide; mainly subadditive (mild antagonistic) effects with 5-**fluorouracil** and cytarabine; and mainly protective (marked antagonistic) effects with vincristine and methotrexate. These findings suggest that SM5887 is suitable for simultaneous administration with bleomycin, etoposide, **doxorubicin**, cisplatin, mitomycin-C, or ifosfamide and not suitable for simultaneous administration with methotrexate. The effects of SM5887 in combination with 5-**fluorouracil**, cytarabine or vincristine may be variable, depending on cell lines. To find optimal combinations, further in vitro and in vivo studies of antitumor activity and toxicity appear to be warranted.

L7 ANSWER 14 OF 18 MEDLINE  
 AN 97049170 MEDLINE  
 DN 97049170 PubMed ID: 8893900  
 TI Paclitaxel combination therapy in the treatment of metastatic breast cancer: a review.  
 AU Holmes F A  
 CS Department of Breast Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston 77030-4009, USA.  
 SO SEMINARS IN ONCOLOGY, (1996 Oct) 23 (5 Suppl 11) 46-56. Ref: 55  
 Journal code: 0420432. ISSN: 0093-7754.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199612  
 ED Entered STN: 19970128  
 Last Updated on STN: 19970128  
 Entered Medline: 19961205  
 AB Combinations of active antineoplastic agents have been the most effective treatment for metastatic breast cancer. Criteria for an effective combination include use of drugs with different mechanisms of action, nonoverlapping toxic effects, and **synergistic**, or at least additive, antitumor activity. Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ), with its unique mechanism of action, offers an excellent opportunity for development of effective combination therapy against breast cancer. However, a number of problems have hindered the

rapid development of effective combinations. The most obvious problem is the lack of a defined optimal dose and schedule of administration. The second problem has been the demonstration of unexpected interactions between paclitaxel and the other component(s) of the combination, often resulting in unusual and serious toxic effects. This review will focus on the phase I and II trials of paclitaxel in combination with established antineoplastic drugs (except **doxorubicin** and congeners, which is covered elsewhere in this issue) for breast cancer: cisplatin, 5-**fluorouracil** with or without folinic acid, cyclophosphamide, radiation therapy, as well as novel investigational agents or strategies, edatrexate, monoclonal antibodies to oncogenes, growth factors, and gene therapy with insertion of multidrug resistance gene into blood stem cells. Combination therapy offers exciting possibilities of enhanced antitumor efficacy. However, given the unexpected and serious toxic effects observed, only proven combinations should be used outside the context of a clinical trial. Additionally, the burden of proof will be to show that these combinations have increased antitumor activity, decreased toxicity, or both compared with single-agent paclitaxel.

L7 ANSWER 15 OF 18 MEDLINE  
 AN 96273138 MEDLINE  
 DN 96273138 PubMed ID: 8702227  
 TI Antitumor activity of menogaril alone, and in combination against human mammary cancer models in mice and rats.  
 AU Yoshida M; Fujioka A; Nakano K; Kobunai T; Saito H; Toko T; Takeda S; Unemi N  
 CS Anticancer and Antimicrobials Research Laboratory, Taiho Pharmaceutical Co., Ltd., Tokushima, Japan.  
 SO ANTICANCER RESEARCH, (1996 May-Jun) 16 (3A) 1155-9.  
 Journal code: 8102988. ISSN: 0250-7005.  
 CY Greece  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199608  
 ED Entered STN: 19960912  
 Last Updated on STN: 19970203  
 Entered Medline: 19960830  
 AB Menogaril is an antitumor agent different from other **anthracyclines** in being active after oral administration. To predict its clinical effectiveness by this route against human breast cancer, we compared its antitumor activity against breast cancer in experimental animals with that of injected Adriamycin. Menogaril had half the much antitumor activity of Adriamycin against human mammary cancer cell lines. Menogaril given orally also had a antitumor activity against mammary cancer caused by 7,12-dimethyl-benz[a]anthracene in rats comparable with that of Adriamycin. The high concentration of menogaril in tumor tissue seemed to contribute to its effectiveness. Of several combinations of cyclophosphamide, Adriamycin, menogaril, and 5-**fluorouracil**, the combination of cyclophosphamide, menogaril, and 5-**fluorouracil** was most effective against mouse leukemia L1210 and human breast cancer xenografts in mice. This combination might have antitumor activity against breast cancer superior to that of the therapy currently of first choice (cyclophosphamide, Adriamycin, and 5-**fluorouracil**) in the clinic.

L7 ANSWER 16 OF 18 MEDLINE  
 AN 96169517 MEDLINE  
 DN 96169517 PubMed ID: 8669796  
 TI [Chemotherapy and cardiotoxicity].  
 Chimiotherapie et cardiotoxicite.  
 AU Brestescher C; Pautier P; Farge D  
 CS Service de Medecine Interne et Pathologie Vasculaire, Hopital Saint-Louis, Paris.

SO ANNALES DE CARDIOLOGIE ET D ANGIOLOGIE, (1995 Oct) 44 (8) 443-7.  
 Journal code: 0142167. ISSN: 0003-3928.  
 CY France  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA French  
 FS Priority Journals  
 EM 199608  
 ED Entered STN: 19960819  
 Last Updated on STN: 19960819  
 Entered Medline: 19960806  
 AB Among the various anticancer drugs, used alone or in combination during  
 courses of chemotherapy, **anthracyclines** (leader:  
**doxorubicin**) are responsible for direct myocardial toxicity, which  
 can exceptionally be acute, but more often chronic with a delayed onset.  
 This cardiotoxicity is directly proportional to the cumulative dose  
 administered and the recommended total dose for **doxorubicin** is  
 550 mg/m<sup>2</sup>. The risk factors able to potentiate cardiotoxicity must be  
 analysed before starting chemotherapy and follow-up by ultrasonography  
 and/or isotope ejection fraction must be repeated before each course. The  
 treatment of **anthracycline**-induced heart failure consists of  
 digitalis alkaloids combined with angiotensin converting enzyme  
 inhibitors. The cardiac toxicity of 5FU is currently explained by the  
 theory of coronary spasm, based on clinical findings such as chest pain  
 associated with ischaemic electrical modifications. The incidence of this  
 toxicity is low, but it can be fatal. Exceptional examples include the  
 cardiotoxicity induced by high-dose cyclophosphamide responsible for acute  
 haemorrhagic myocarditis, potentiation of the cardiotoxic effect of  
**anthracyclines** by dacarbazine and plicamycin, and serious  
 ventricular and supraventricular arrhythmias induced by amsacrine. Among  
 the various cytokines used in oncology, interferon is responsible for  
 heart failure, reversible after stopping treatment, but also for  
 ventricular arrhythmias, or even sudden death, the pathophysiology of  
 which still remains unclear.

L7 ANSWER 17 OF 18 MEDLINE  
 AN 90381585 MEDLINE  
 DN 90381585 PubMed ID: 2119245  
 TI Modulation of the effect of **anthracycline** efficacy and toxicity  
 by ICRF-187.  
 AU Blum R H; Walsh C; Green M D; Speyer J L  
 CS Division of Medical Oncology, Kaplan Cancer Center, New York University  
 Medical Center, New York 10016.  
 NC CA 16087 (NCI)  
 R01 CA 36524 (NCI)  
 SO CANCER INVESTIGATION, (1990) 8 (2) 267-8.  
 Journal code: 8307154. ISSN: 0735-7907.  
 CY United States  
 DT (CLINICAL TRIAL)  
 Journal; Article; (JOURNAL ARTICLE)  
 (RANDOMIZED CONTROLLED TRIAL)  
 LA English  
 FS Priority Journals  
 EM 199010  
 ED Entered STN: 19901122  
 Last Updated on STN: 19901122  
 Entered Medline: 19901024

L7 ANSWER 18 OF 18 MEDLINE  
 AN 85016694 MEDLINE  
 DN 85016694 PubMed ID: 6484579  
 TI Biologic and biochemical effects of mitoxantrone.  
 AU Durr F E  
 SO SEMINARS IN ONCOLOGY, (1984 Sep) 11 (3 Suppl 1) 3-10.  
 Journal code: 0420432. ISSN: 0093-7754.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 198411  
ED Entered STN: 19900320  
Last Updated on STN: 19900320  
Entered Medline: 19841101

AB Mitoxantrone (1,4-dihydroxy-5,8-bis[(2-[(2-hydroxyethyl)-amino]-ethyl)amino]-9,10-anthracenedione dihydrochloride) is a representative of a new class of chemical compounds with antineoplastic activity. It was one of a number of polycyclic aromatic compounds tested at the American Cyanamid Laboratories and was the most effective and potent derivative synthesized. Mitoxantrone produced significant increases in life span and long-term survivors when tested against P388 and L1210 leukemias, B16 melanoma, and colon tumor 26 transplanted into mice. In comparative animal trials, it proved more effective than most of the other agents tested, including **doxorubicin**, cyclophosphamide, methotrexate, cytarabine, and 5-**fluorouracil**. It was also active against intravenously implanted L1210 leukemia, in contrast to **doxorubicin**, though this is considered to have a similar mode of action. Mitoxantrone also demonstrated moderate activity against sublines of the mouse leukemias, which were resistant to **anthracyclines**. Significant therapeutic **synergism** against P388 leukemia was observed when mitoxantrone was administered on the same day as methotrexate and cytarabine or in sequence with cyclophosphamide, cisplatin, or vincristine sulfate. Mitoxantrone is active intraperitoneally, intramuscularly, subcutaneously, and intravenously, but oral activity has not been demonstrated. Although dose schedule did not appear critical, treatment every 4 days X 3 appeared to be the most effective. The mechanism of action of mitoxantrone has not been fully elucidated, but it is known to inhibit DNA and RNA synthesis. In cell culture, mitoxantrone induces nuclear aberrations with chromosomal scattering and morphologic alterations similar to those induced by **doxorubicin**. Drug-induced cell kill was not phase specific. Experiments with a resistant human colon carcinoma cell line (WiDr) indicated that resistance may be due to alterations of the cell membrane with decreased uptake. Mitoxantrone has markedly less cardiotoxicity than **doxorubicin**, and this may be linked to the fact that the drug does not induce free radical formation but inhibits lipid peroxidation.

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HIGHEST APPLICATION PUBLICATION NUMBER: US2002174474  
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REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2002  
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=> s l4 and (gemcitabine or fluoropyrimidine or fluorouracil or cytidine)
    1096 ANTHRACYCLINE
    1190 ANTHRACYCLINES
    1863 ANTHRACYCLINE
        (ANTHRACYCLINE OR ANTHRACYCLINES)
    2837 DAUNORUBICIN
    13 DAUNORUBICINS
    2841 DAUNORUBICIN
        (DAUNORUBICIN OR DAUNORUBICINS)
    4729 DOXORUBICIN
    14 DOXORUBICINS
    4729 DOXORUBICIN
        (DOXORUBICIN OR DOXORUBICINS)
    48796 SYNERG?
    385 GEMCITABINE
    317 FLUOROPYRIMIDINE
    121 FLUOROPYRIMIDINES
    407 FLUOROPYRIMIDINE
        (FLUOROPYRIMIDINE OR FLUOROPYRIMIDINES)
    5893 FLUOROURACIL
    22 FLUOROURACILS
    5896 FLUOROURACIL
        (FLUOROURACIL OR FLUOROURACILS)
    3715 CYTIDINE
    118 CYTIDINES
    3747 CYTIDINE
        (CYTIDINE OR CYTIDINES)
L8      221 L4 AND (GEMCITABINE OR FLUOROPYRIMIDINE OR FLUOROURACIL OR CYTID
        INE)

=> s l8 and treat?
    810071 TREAT?
L9      221 L8 AND TREAT?

=> s l9 and method
    1795812 METHOD
    1014077 METHODS
    1912153 METHOD
        (METHOD OR METHODS)
L10     221 L9 AND METHOD

=> s l10 and combin?
    1724689 COMBIN?
L11     221 L10 AND COMBIN?

=> s l11 and analog?
    446691 ANALOG?

```

L12 212 L11 AND ANALOG?

=> dis 112 200-212 bib abs

L12 ANSWER 200 OF 212 USPATFULL

AN 1998:57724 USPATFULL

TI Human carbonyl reductase

IN Hillman, Jennifer L., San Jose, CA, United States

Goli, Surya K., Sunnyvale, CA, United States

PA Incyte Pharmaceuticals, Inc., Palo, CA, United States (U.S. corporation)

PI US 5756299 19980526

AI US 1996-762129 19961209 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Patterson, Jr., Charles L.

LREP Billings, Lucy J.

CLMN Number of Claims: 11

ECL Exemplary Claim: 1

DRWN 8 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 2007

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a human carbonyl reductase (HCRD) and polynucleotides which identify and encode HCRD. The invention also provides genetically engineered expression vectors and host cells comprising the nucleic acid sequences encoding HCRD and a **method** for producing HCRD. The invention also provides for agonists, antibodies, or antagonists specifically binding HCRD, and their use, in the prevention and **treatment** of diseases associated with expression of HCRD. Additionally, the invention provides for the use of antisense molecules to polynucleotides encoding HCRD for the **treatment** of diseases associated with the expression of HCRD. The invention also provides diagnostic assays which utilize the polynucleotide, or fragments or the complement thereof, and antibodies specifically binding HCRD.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 201 OF 212 USPATFULL

AN 1998:45195 USPATFULL

TI **Combination** for **treatment** of proliferative diseases

IN Muller, Marcel, Allschwil, Switzerland

Geiger, Thomas, Freiburg, Germany, Federal Republic of

Altmann, Karl-Heinz, Reinach, Switzerland

Fabbro, Dorian, Arlesheim, Switzerland

Dean, Nicholas M., Encinitas, CA, United States

Monia, Brett, Carlsbad, CA, United States

Bennett, Clarence Frank, Carlsbad, CA, United States

PA Novartis Corporation, Summit, NJ, United States (U.S. corporation)

PI US 5744460 19980428

AI US 1996-612775 19960307 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Robinson, Douglas W.; Assistant Examiner: Nelson, Amy J.

LREP Nowak, Henry P.

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2910

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to **combinations** of PKC-targeted (especially PKC-.alpha.-targeted) deoxyribo- and ribo-oligonucleotides and derivatives thereof with other chemotherapeutic compounds, as well as to pharmaceutical preparations and/or therapies, in relation to

disease states which respond to such oligonucleotides or oligonucleotide derivatives, especially to to modulation of the activity of a regulatory protein. In particular, the invention relates to products or **combinations** comprising antisense oligonucleotides or oligonucleotide derivatives targeted to nucleic acids encoding human PKC and other (preferably standard) chemotherapeutics, either in fixed **combination** or for chronologically staggered or simultaneous administration, and the **combined** use of both classes of compounds, either in fixed **combination** or for chronologically staggered or simultaneous administration, for the **treatment** of proliferative diseases, especially tumor diseases, that can be **treated** by inhibition of PKC activity, that is, where the antisense oligonucleotides or oligonucleotide derivatives are targeted to nucleic acids encoding the regulatory protein PKC or active mutated derivatives thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 202 OF 212 USPATFULL  
AN 1998:4744 USPATFULL  
TI Thioether conjugates  
IN Willner, David, Hamden, CT, United States  
Trail, Pamela A., Farmington, CT, United States  
King, H. Dalton, Hamden, CT, United States  
Hofstead, Sandra J., Middletown, CT, United States  
Greenfield, Robert S., Wallingford, CT, United States  
Braslawsky, Gary R., Glastonbury, CT, United States  
PA Bristol-Myers Squibb Company, Princeton, NJ, United States (U.S. corporation)  
PI US 5708146 19980113  
AI US 1995-469840 19950606 (8)  
RLI Division of Ser. No. US 1992-824951, filed on 23 Jan 1992, now patented, Pat. No. US 5622929  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Peselev, Elli  
LREP Poor, Brian, Sorrentino, Joseph M., Savitsky, Thomas R.  
CLMN Number of Claims: 13  
ECL Exemplary Claim: 1  
DRWN 18 Drawing Figure(s); 17 Drawing Page(s)  
LN.CNT 2044

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided are drug/ligand compounds of Formula (I): ##STR1## (I) in which

D is a drug moiety;

n is an integer from 1 to 10;

p is an integer from 1 to 6;

Y is O or NH.sub.2.sup.+ Cl.sup.- ;

z is 0 or 1;

q is about 1 to about 10;

X is a ligand; and,

A is a Michael Addition Adduct.

In a preferred embodiment, the ligand is an immunoglobulin, preferably a chimeric antibody or fragment thereof. Also provided are formulations comprising as an active ingredient a compound of Formula (I), intermediates useful for preparing the compounds of Formula (I),

processes for preparing the compounds of Formula (I), and  
**methods** for using the compounds of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 203 OF 212 USPATFULL  
AN 97:104147 USPATFULL  
TI Poly-.beta.-1.fwdarw.4-N-acetylucosamine copolymer composition with collagen  
IN Vournakis, John N., Hanover, NH, United States  
Finkielsztejn, Sergio, Chestnut Hill, MA, United States  
Pariser, Ernest R., Belmont, MA, United States  
Helton, Mike, Memphis, TN, United States  
PA Marine Polymer Technologies, Inc., Danvers, MA, United States (U.S. corporation)  
PI US 5686115 19971111  
AI US 1995-470912 19950606 (8)  
RLI Continuation-in-part of Ser. No. US 1994-347911, filed on 1 Dec 1994, now patented, Pat. No. US 5623064 which is a continuation-in-part of Ser. No. US 1993-160569, filed on 1 Dec 1993, now patented, Pat. No. US 5622834  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Kight, John; Assistant Examiner: Fonda, Kathleen Kahler  
LREP Pennie & Edmonds  
CLMN Number of Claims: 20  
ECL Exemplary Claim: 1  
DRWN 72 Drawing Figure(s); 58 Drawing Page(s)  
LN.CNT 4073

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a purified, easily produced poly-.beta.-1.fwdarw.4-N-acetylglucosamine (p-GlcNAc) polysaccharide species useful in collagen copolymers. The p-GlcNAc of the invention is a polymer of high molecular weight whose constituent monosaccharide sugars are attached in a .beta.-1.fwdarw.4 conformation, and which is free of proteins, and substantially free of single amino acids, and other organic and inorganic contaminants. In addition, derivatives and reformulations of p-GlcNAc are described. The present invention further relates to **methods** for the purification of the p-GlcNAc of the invention from microalgae, preferably diatom, starting sources. Still further, the invention relates to **methods** for the derivatization and reformulation of the p-GlcNAc. Additionally, the present invention relates to the uses of pure p-GlcNAc, its derivatives, and/or its reformulations.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 204 OF 212 USPATFULL  
AN 97:75816 USPATFULL  
TI Antibodies that bind to endoglin  
IN Thorpe, Philip E., Dallas, TX, United States  
Burrows, Francis J., San Diego, CA, United States  
PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)  
PI US 5660827 19970826  
AI US 1995-457229 19950601 (8)  
RLI Division of Ser. No. US 1994-350212, filed on 5 Dec 1994 which is a continuation-in-part of Ser. No. US 1994-205330, filed on 2 Mar 1994 which is a continuation-in-part of Ser. No. US 1994-295868, filed on 6 Sep 1994 which is a continuation-in-part of Ser. No. US 1992-846349, filed on 5 Mar 1992, now abandoned  
DT Utility  
FS Granted



EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Ebert, Ray F.  
LREP Arnold, White & Durkee  
CLMN Number of Claims: 30  
ECL Exemplary Claim: 1,16  
DRWN 37 Drawing Figure(s); 25 Drawing Page(s)  
LN.CNT 5787

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are antibodies that specifically bind to endoglin. Conjugates of the antibodies linked to diagnostic or therapeutic agents are also provided. **Methods** of using the antibodies and conjugates are also disclosed, including **methods** of targeting the vasculature of solid tumors through recognition of the tumor vasculature-associated antigen, endoglin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 205 OF 212 USPATFULL  
AN 97:61697 USPATFULL  
TI Diarylalkyl piperidines useful as multi-drug resistant tumor agents  
IN Sunkara, Sai P., San Diego, CA, United States  
Freedman, Jules, Cincinnati, OH, United States  
PA Merrell Pharmaceuticals Inc., Cincinnati, OH, United States (U.S. corporation)  
PI US 5648365 19970715  
WO 9417040 19940804  
AI US 1996-481538 19960311 (8)  
WO 1993-US12300 19931217  
19960311 PCT 371 date  
19960311 PCT 102(e) date  
RLI Continuation of Ser. No. US 1993-111027, filed on 24 Aug 1993, now abandoned which is a continuation of Ser. No. US 1993-6569, filed on 21 Jan 1993, now abandoned  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Raymond, Richard L.  
LREP Lentz, Nelsen L.  
CLMN Number of Claims: 6  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 461

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Diarylalkyl piperidines of formula (1) ##STR1## reverse drug resistance in multi-drug resistant tumors. These compounds apparently function by inhibiting a p-glycoprotein pump which becomes activated in late stage tumor development and which is inherently present in tumors from certain origins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 206 OF 212 USPATFULL  
AN 97:47398 USPATFULL  
TI **Methods** and compositions for poly-.beta.-1-4-N-acetylglucosamine chemotherapeutics  
IN Vournakis, John N., Hanover, NH, United States  
Finkielsztejn, Sergio, Chestnut Hill, MA, United States  
Pariser, Ernest R., Belmont, MA, United States  
Helton, Mike, Memphis, TN, United States  
PA Marine Polymer Technologies, Inc., Danvers, MA, United States (U.S. corporation)  
PI US 5635493 19970603  
AI US 1995-471545 19950606 (8)  
RLI Continuation-in-part of Ser. No. US 1994-347911, filed on 1 Dec 1994 which is a continuation-in-part of Ser. No. US 1993-160569, filed on 1 Dec 1993

DT Utility  
FS Granted  
EXNAM Primary Examiner: Kight, John; Assistant Examiner: Fonda, Kathleen  
Kahler  
LREP Pennie & Edmonds  
CLMN Number of Claims: 16  
ECL Exemplary Claim: 1  
DRWN 73 Drawing Figure(s); 58 Drawing Page(s)  
LN.CNT 3937

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a purified, easily produced poly-.beta.-1.fwdarw.4-N-acetylglucosamine (p-GlcNAc) polysaccharide species useful in drug compositions. The p-GlcNAc of the invention is a polymer of high molecular weight whose constituent monosaccharide sugars are attached in a .beta.-1.fwdarw.4 conformation, and which is free of proteins, and substantially free of single amino acids, and other organic and inorganic contaminants. In addition, derivatives and reformulations of p-GlcNAc are described. The present invention further relates to **methods** for the purification of the p-GlcNAc of the invention from microalgae, preferably diatom, starting sources. Still further, the invention relates to **methods** for the derivatization and reformulation of the p-GlcNAc. Additionally, the present invention relates to the uses of pure p-GlcNAc, its derivatives, and/or its reformulations.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 207 OF 212 USPATFULL

AN 97:35944 USPATFULL

TI **Methods** and compositions for poly-.beta.-1-4-N-acetylglucosamine biological barriers

IN Vournakis, John N., Hanover, NH, United States  
Finkielsztejn, Sergio, Chestnut Hill, MA, United States  
Pariser, Ernest R., Belmont, MA, United States  
Helton, Mike, Memphis, TN, United States

PA Marine Polymer Technologies, Inc., Danvers, MA, United States (U.S. corporation)

PI US 5624679 19970429

AI US 1995-470083 19950606 (8)

RLI Continuation-in-part of Ser. No. US 1994-347911, filed on 1 Dec 1994 which is a continuation-in-part of Ser. No. US 1993-160569, filed on 1 Dec 1993

DT Utility

FS Granted

EXNAM Primary Examiner: Kight, John; Assistant Examiner: Fonda, Kathleen  
Kahler

LREP Pennie & Edmonds

CLMN Number of Claims: 14

ECL Exemplary Claim: 1

DRWN 74 Drawing Figure(s); 58 Drawing Page(s)

LN.CNT 4072

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a purified, easily produced poly-.beta.-1.fwdarw.4-N-acetylglucosamine (p-GlcNAc) polysaccharide species. The p-GlcNAc of the invention is a polymer of high molecular weight whose constituent monosaccharide sugars are attached in a .beta.-1.fwdarw.4 conformation, and which is free of proteins, and substantially free of single amino acids, and other organic and inorganic contaminants. In addition, derivatives and reformulations of p-GlcNAc are described. The present invention further relates to **methods** for the purification of the p-GlcNAc of the invention from microalgae, preferably diatom, starting sources. Still further, the invention relates to **methods** for the derivatization and reformulation of the p-GlcNAc. Additionally, the present invention

relates to the uses of pure p-GlcNAc, its derivatives, and/or its reformulations.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 208 OF 212 USPATFULL  
AN 97:33724 USPATFULL  
TI Thioether conjugates  
IN Willner, David, Hamden, CT, United States  
Trail, Pamela A., Farmington, CT, United States  
King, H. Dalton, Hamden, CT, United States  
Hofstead, Sandra J., Middletown, CT, United States  
Greenfield, Robert S., Wallingford, CT, United States  
Braslawsky, Gary R., Glastonbury, CT, United States  
PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)  
PI US 5622929 19970422  
AI US 1992-824951 19920123 (7)  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Peselev, Elli  
LREP Bristol-Myers Squibb Co.  
CLMN Number of Claims: 52  
ECL Exemplary Claim: 6  
DRWN 18 Drawing Figure(s); 17 Drawing Page(s)  
LN.CNT 2212  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Provided are drug/ligand compounds of Formula (I): ##STR1## in which D is a drug moiety;

n is an integer from 1 to 10;

p is an integer from 1 to 6;

Y is O or NH.sub.2.sup.+ Cl.sup.- ;

z is 0 or 1;

q is about 1 to about 10;

X is a ligand; and,

A is a Michael Addition Adduct.

In a preferred embodiment, the ligand is an immunoglobulin, preferably a chimeric antibody or fragment thereof. Also provided are formulations comprising as an active ingredient a compound of Formula (I), intermediates useful for preparing the compounds of Formula (I), processes for preparing the compounds of Formula (I), and **methods** for using the compounds of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 209 OF 212 USPATFULL  
AN 97:16169 USPATFULL  
TI Thioether conjugates  
IN Willner, David, Hamden, CT, United States  
Trail, Pamela A., Farmington, CT, United States  
King, H. Dalton, Hamden, CT, United States  
Hofstead, Sandra J., Middletown, CT, United States  
Greenfield, Robert S., Wallingford, CT, United States  
Braslawsky, Gary R., Glastonbury, CT, United States  
PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)

PI US 5606017 19970225  
AI US 1995-468162 19950606 (8)  
RLI Division of Ser. No. US 1992-824951, filed on 23 Jan 1992  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Peselev, Elli  
CLMN Number of Claims: 20  
ECL Exemplary Claim: 1  
DRWN 18 Drawing Figure(s); 17 Drawing Page(s)  
LN.CNT 2095  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Provided are drug/ligand compounds of Formula (I): ##STR1## in which D  
is a drug moiety;

n is an integer from 1 to 10;

p is an integer from 1 to 6;

Y is O or NH.sub.2.sup.+ Cl.sup.- ;

z is 0 or 1;

q is about 1 to about 10;

X is a ligand; and,

A is a Michael Addition Adduct.

In a preferred embodiment, the ligand is an immunoglobulin, preferably a chimeric antibody or fragment thereof. Also provided are formulations comprising as an active ingredient a compound of Formula (I), intermediates useful for preparing the compounds of Formula (I), processes for preparing the compounds of Formula (I), and **methods** for using the compounds of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 210 OF 212 USPATFULL  
AN 95:110215 USPATFULL  
TI Preparation and use of steroid-polyanionic polymer-based conjugates targeted to vascular endothelial cells  
IN Thorpe, Philip E., Dallas, TX, United States  
PA UT SW Medical CTR at Dallas, Dallas, TX, United States (U.S. corporation)  
PI US 5474765 19951212  
AI US 1992-856018 19920323 (7)  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Kishore, Gollamudi; Assistant Examiner: Kulkosky, Peter F.  
LREP Arnold, White & Durkee  
CLMN Number of Claims: 24  
ECL Exemplary Claim: 1  
DRWN 14 Drawing Figure(s); 14 Drawing Page(s)  
LN.CNT 2175  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB This invention discloses new targeted conjugates for the delivery of a compound, and particularly, a steroid, to vascular endothelial cells. The conjugates comprise two components, preferably linked by a selectively-hydrolyzable bond, such as an acid-labile bond or enzyme-sensitive bond. The first component, a polyanionic polymer, and preferably, a polysulphated polymer such as a heparin-derivative, specifically directs the conjugate to vascular endothelial cells. The second component is a selected agent, such as asteroid, which exerts a

specific effect on the target cell following its release. In particular, the present invention provides novel conjugated angiogenesis inhibitors, for use in the **treatment** of pathogenic conditions including cancer, arthritis, and diabetic blindness. An inhibitor comprising a heparin derivative and the anti-angiogenic steroid, cortisol, is herein shown to be markedly acid-labile, to suppress DNA synthesis and cell migration in human umbilical vein endothelial cells, to retard or abolish (depending on the route of injection) the vascularization of sponges in vivo and to retard lung tumor growth in mice by 65%. No adverse effects of the conjugate were detected, and equivalent **treatments** with a mixture of heparin plus cortisol were significantly less effective in all cases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 211 OF 212 USPATFULL  
 AN 89:82404 USPATFULL  
 TI Pharmaceutical compositions having antineoplastic activity  
 IN Tognella, Sergio, Milan, Italy  
 Tedeschi, Michele, Milan, Italy  
 Assereto, Roberto, Milan, Italy  
 Tofanetti, Odoardo, Milan, Italy  
 Cavalletti, Ennio, Milan, Italy  
 PA Boehringer Biochemia Robin SpA, Milan, Italy (non-U.S. corporation)  
 PI US 4871528 19891003  
 AI US 1987-105169 19871007 (7)  
 RLI Continuation-in-part of Ser. No. US 1987-102746, filed on 24 Sep 1987, now abandoned which is a continuation of Ser. No. US 1986-857344, filed on 30 Apr 1986, now abandoned  
 PRAI IT 1986-21925 19861007  
 IT 1987-48339 19870901  
 DT Utility  
 FS Granted  
 EXNAM Primary Examiner: Robinson, Douglas W.; Assistant Examiner: Kearse, Richard  
 LREP Armstrong, Nikaido, Marmelstein, Kubovcik & Murray  
 CLMN Number of Claims: 18  
 ECL Exemplary Claim: 1  
 DRWN 2 Drawing Figure(s); 1 Drawing Page(s)  
 LN.CNT 826

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Pharmaceutical compositions containing unit or separate dosages of 2.5 to 5 grams of reduced glutathione (GSH) and known anti-tumor agents, to be used simultaneously, separately or sequentially in anti-tumor therapy.

Compounds of the invention, that can be used both in mono- or polychemotherapy, reach surprising results against tumors, thus avoiding the onset of dangerous side-effects, such as nephrotoxicity induced by cisplatinum, and increasing the long term survival rates.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 212 OF 212 USPATFULL  
 AN 89:74162 USPATFULL  
 TI **Treatment** of cancer  
 IN Amagase, Harunobu, Hiroshima, Japan  
 Arakawa, Masato, Hiroshima, Japan  
 Hashimoto, Ken, Hiroshima, Japan  
 PA Wakunaga Seiyaku Kabushiki Kaisha, Osaka, Japan (non-U.S. corporation)  
 PI US 4863902 19890905  
 AI US 1986-935740 19861128 (6)  
 PRAI JP 1985-268174 19851128  
 JP 1985-268175 19851128

JP 1986-116557 19860521  
JP 1986-116558 19860521  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Phillips, Delbert R.  
LREP Oblon, Spivak, McClelland, Maier & Neustadt  
CLMN Number of Claims: 62  
ECL Exemplary Claim: 1  
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)  
LN.CNT 2990

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Antitumor effect of antitumor agents or **treatments** is favorably controlled by a growth factor. The growth factor enhances antitumor actions of antitumor agents or **treatments** including those against which tumor or cancer has acquired resistant, or reduces side effects due to the antitumor agents or **treatments**. The most typical growth factors include human epidermal growth factor. A lot of tumors or cancers including human ones has been tested and a lot of growth factors has been tested, and the favorable control has been determined.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> dis 19 1-20 bib abs

L9 ANSWER 1 OF 221 USPATFULL  
AN 2002:308381 USPATFULL  
TI Urea compounds and methods of uses  
IN Santora, Vincent, Thousand Oaks, CA, UNITED STATES  
Askew, Benny, Newbury Park, CA, UNITED STATES  
Ghose, Arup, Thousand Oaks, CA, UNITED STATES  
Hague, Andrew, Camarillo, CA, UNITED STATES  
Kim, Tae Seong, Thousand Oaks, CA, UNITED STATES  
Laber, Ellen, Ventura, CA, UNITED STATES  
Li, Aiwen, Newbury Park, CA, UNITED STATES  
Lian, Brian, Bloomington, IN, UNITED STATES  
Liu, Gang, Oak Park, CA, UNITED STATES  
Norman, Mark, Thousand Oaks, CA, UNITED STATES  
Smith, Leon, Somerset, NJ, UNITED STATES  
Tasker, Andrew, Simi Valley, CA, UNITED STATES  
Tegley, Christopher, Thousand Oaks, CA, UNITED STATES  
Yang, Kevin, San Gabriel, CA, UNITED STATES  
PI US 2002173507 A1 20021121  
AI US 2001-930753 A1 20010814 (9)  
PRAI US 2000-225793P 20000815 (60)  
DT Utility  
FS APPLICATION  
LREP AMGEN INCORPORATED, MAIL STOP 27-4-A, ONE AMGEN CENTER DRIVE, THOUSAND OAKS, CA, 91320-1799  
CLMN Number of Claims: 36  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 7251  
AB Selected novel urea compounds are effective for prophylaxis and **treatment** of diseases, such as cell proliferation or apoptosis mediated diseases. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and **treatment** of diseases and other maladies or conditions involving stroke, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

L9 ANSWER 2 OF 221 USPATFULL  
 AN 2002:308336 USPATFULL  
 TI Methods for enhancing the efficacy of cancer therapy  
 IN Pennica, Diane, Burlingame, CA, UNITED STATES  
 Polakis, Paul, Burlingame, CA, UNITED STATES  
 Szeto, Wayne, San Francisco, CA, UNITED STATES  
 Tice, David, San Mateo, CA, UNITED STATES  
 PI US 2002173461 A1 20021121  
 AI US 2001-901812 A1 20010710 (9)  
 PRAI US 2000-228914P 20000829 (60)  
 US 2000-175849P 20000113 (60)  
 US 2000-197089P 20000414 (60)  
 DT Utility  
 FS APPLICATION  
 LREP KNOBBE MARTENS OLSON & BEAR LLP, 620 NEWPORT CENTER DRIVE, SIXTEENTH  
 FLOOR, NEWPORT BEACH, CA, 92660  
 CLMN Number of Claims: 66  
 ECL Exemplary Claim: 1  
 DRWN 47 Drawing Page(s)  
 LN.CNT 4875  
 AB The invention concerns the identification of tumor antigens the  
 expression of which is selectively upregulated by retinoid  
**treatment**. The invention further concerns improved methods of  
 cancer **treatment** and, in particular, methods enhancing the  
 efficacy of the **treatment** of cancers characterized by aberrant  
 Wnt signaling by administration of retinoic acid or other retinoids.

L9 ANSWER 3 OF 221 USPATFULL  
 AN 2002:308329 USPATFULL  
 TI Nucleic acids, proteins, and antibodies  
 IN Rosen, Craig A., Laytonsville, MD, UNITED STATES  
 Ruben, Steven M., Olney, MD, UNITED STATES  
 Barash, Steven C., Rockville, MD, UNITED STATES  
 PI US 2002173454 A1 20021121  
 AI US 2001-764904 A1 20010117 (9)  
 PRAI US 2000-179065P 20000131 (60)  
 US 2000-180628P 20000204 (60)  
 US 2000-214886P 20000628 (60)  
 US 2000-217487P 20000711 (60)  
 US 2000-225758P 20000814 (60)  
 US 2000-220963P 20000726 (60)  
 US 2000-217496P 20000711 (60)  
 US 2000-225447P 20000814 (60)  
 US 2000-218290P 20000714 (60)  
 US 2000-225757P 20000814 (60)  
 US 2000-226868P 20000822 (60)  
 US 2000-216647P 20000707 (60)  
 US 2000-225267P 20000814 (60)  
 US 2000-216880P 20000707 (60)  
 US 2000-225270P 20000814 (60)  
 US 2000-251869P 20001208 (60)  
 US 2000-235834P 20000927 (60)  
 US 2000-234274P 20000921 (60)  
 US 2000-234223P 20000921 (60)  
 US 2000-228924P 20000830 (60)  
 US 2000-224518P 20000814 (60)  
 US 2000-236369P 20000929 (60)  
 US 2000-224519P 20000814 (60)  
 US 2000-220964P 20000726 (60)  
 US 2000-241809P 20001020 (60)  
 US 2000-249299P 20001117 (60)  
 US 2000-236327P 20000929 (60)  
 US 2000-241785P 20001020 (60)

US 2000-244617P	20001101 (60)
US 2000-225268P	20000814 (60)
US 2000-236368P	20000929 (60)
US 2000-251856P	20001208 (60)
US 2000-251868P	20001208 (60)
US 2000-229344P	20000901 (60)
US 2000-234997P	20000925 (60)
US 2000-229343P	20000901 (60)
US 2000-229345P	20000901 (60)
US 2000-229287P	20000901 (60)
US 2000-229513P	20000905 (60)
US 2000-231413P	20000908 (60)
US 2000-229509P	20000905 (60)
US 2000-236367P	20000929 (60)
US 2000-237039P	20001002 (60)
US 2000-237038P	20001002 (60)
US 2000-236370P	20000929 (60)
US 2000-236802P	20001002 (60)
US 2000-237037P	20001002 (60)
US 2000-237040P	20001002 (60)
US 2000-240960P	20001020 (60)
US 2000-239935P	20001013 (60)

DT Utility

FS APPLICATION

LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 21956

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel reproductive system related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "reproductive system related antigens," and the use of such reproductive system related antigens for detecting disorders of the reproductive system, particularly the presence of cancers and cancer metastases. More specifically, isolated reproductive system associated nucleic acid molecules are provided encoding novel reproductive system associated polypeptides. Novel reproductive system related polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human reproductive system associated polynucleotides and/or polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, **treating**, preventing and/or prognosing disorders related to the reproductive system, including reproductive system cancers, and therapeutic methods for **treating** such disorders. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and function of the polypeptides of the present invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 4 OF 221 USPATFULL

AN 2002:307870 USPATFULL

TI 28 human secreted proteins

IN Ruben, Steven M., Olney, MD, UNITED STATES  
 Rosen, Craig A., Laytonsville, MD, UNITED STATES  
 Li, Yi, Sunnyvale, CA, UNITED STATES  
 Zeng, Zhizhen, Lansdale, PA, UNITED STATES  
 Kyaw, Hla, Frederick, MD, UNITED STATES  
 Fischer, Carrie L., Burke, VA, UNITED STATES  
 Li, Haodong, Gaithersburg, MD, UNITED STATES



Soppet, Daniel R., Centreville, VA, UNITED STATES  
 Gentz, Reiner L., Rockville, MD, UNITED STATES  
 Wei, Ying-Fei, Berkeley, CA, UNITED STATES  
 Moore, Paul A., Germantown, MD, UNITED STATES  
 Young, Paul E., Gaithersburg, MD, UNITED STATES  
 Greene, John M., Gaithersburg, MD, UNITED STATES  
 Ferrie, Ann M., Tewksbury, MA, UNITED STATES  
 PI US 2002172994 A1 20021121  
 AI US 2001-852797 A1 20010511 (9)  
 RLI Continuation-in-part of Ser. No. US 1998-152060, filed on 11 Sep 1998,  
 PENDING Continuation-in-part of Ser. No. WO 1998-US4858, filed on 12 Mar  
 1998, UNKNOWN  
 PRAI US 2001-265583P 20010202 (60)  
 US 1997-40762P 19970314 (60)  
 US 1997-40710P 19970314 (60)  
 US 1997-50934P 19970530 (60)  
 US 1997-48100P 19970530 (60)  
 US 1997-48357P 19970530 (60)  
 US 1997-48189P 19970530 (60)  
 US 1997-57765P 19970905 (60)  
 US 1997-48970P 19970606 (60)  
 US 1997-68368P 19971219 (60)  
 DT Utility  
 FS APPLICATION  
 LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850  
 CLMN Number of Claims: 23  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 17794  
 AB The present invention relates to novel human secreted proteins and  
 isolated nucleic acids containing the coding regions of the genes  
 encoding such proteins. Also provided are vectors, host cells,  
 antibodies, and recombinant methods for producing human secreted  
 proteins. The invention further relates to diagnostic and therapeutic  
 methods useful for diagnosing and **treating** diseases,  
 disorders, and/or conditions related to these novel human secreted  
 proteins.

L9 ANSWER 5 OF 221 USPATFULL  
 AN 2002:303975 USPATFULL  
 TI Tumor suppressor designated TS10q23.3  
 IN Steck, Peter, Bellaire, TX, United States  
 Pershouse, Mark A., Houston, TX, United States  
 Jasser, Samar A., Houston, TX, United States  
 Yung, Alfred W. K., Houston, TX, United States  
 Tavtigian, Sean V., Salt Lake City, UT, United States  
 PA Myriad Genetics, Inc., Salt Lake City, UT, United States (U.S.  
 corporation)  
 Board of Regents, University of Texas System, Austin, TX, United States  
 (U.S. corporation)  
 PI US 6482795 B1 20021119  
 AI US 1998-140749 19980826 (9)  
 RLI Continuation-in-part of Ser. No. US 1997-719115, filed on 30 Jan 1997  
 PRAI US 1997-57750P 19970826 (60)  
 US 1998-83563P 19980430 (60)  
 DT Utility  
 FS GRANTED  
 EXNAM Primary Examiner: Caputa, Anthony C.; Assistant Examiner: Canella, Karen  
 A.  
 LREP Rothwell, Figg, Ernst & Manbeck, PC  
 CLMN Number of Claims: 4  
 ECL Exemplary Claim: 1  
 DRWN 51 Drawing Figure(s); 43 Drawing Page(s)

LN.CNT 7289

AB A specific region of chromosome 10 (10q23.3) has been implicated by series of studies to contain a tumor suppressor gene involved in gliomas, as well as a number of other human cancers. One gene within this region was identified, and the corresponding coding region of the gene represents a novel 47 kD protein. A domain of this product has an exact match to the conserved catalytic domain of protein tyrosine phosphatases, indicating a possible functional role in phosphorylation events. Sequence analyses demonstrated the a number of exons of the gene were deleted in tumor cell lines used to define the 10q23.3 region, leading to the classification of this gene as a tumor suppressor. Further analyses have demonstrated the presence of a number of mutations in the gene in both glioma and prostate carcinoma cells. Methods for diagnosing and **treating** cancers related to this tumor suppressor, designated as TS10q23.3, also are disclosed.

L9 ANSWER 6 OF 221 USPATFULL

AN 2002:301590 USPATFULL

TI Method of **treating** hematologic tumors and cancers

IN Pardee, Arthur B., Cambridge, MA, UNITED STATES

Anderson, Kenneth, Wellesley, MA, UNITED STATES

Gupta, Deepak, Norwood, MA, UNITED STATES

Li, Chiang, West Roxbury, MA, UNITED STATES

Li, Youzhi, Dedham, MA, UNITED STATES

PI US 2002169135 A1 20021114

AI US 2001-7352 A1 20011107 (10)

PRAI US 2000-246552P 20001107 (60)

DT Utility

FS APPLICATION

LREP Ivor R. Elrifi, Ph.D., Esq., Mintz, Levin, Cohn, Ferris,, Glovsky and Popeo, P.C., One Financial Center, Boston, MA, 02111

CLMN Number of Claims: 111

ECL Exemplary Claim: 1

DRWN 5 Drawing Page(s)

LN.CNT 1286

AB Multiple myeloma and other hematologic tumors and/or malignancies can be **treated** by administration of a G1 and/or S phase drug, which is preferably .beta.-lapachone, or a derivative or analog thereof, combined with a G2/M phase drug such as a taxane derivative, which is advantageously paclitaxel. This combination of the G1 and/or S phase drug with the G2/M phase drug results in an unexpectedly greater than additive (i.e., **synergistic**) apoptosis in multiple myeloma cells. The invention includes methods of **treating** multiple myeloma by administering the combination of the G1 and/or S phase drug and the G2/M phase drug, pharmaceutical compositions comprising the combination of drugs used in these methods, as well as pharmaceutical kits.

L9 ANSWER 7 OF 221 USPATFULL

AN 2002:301185 USPATFULL

TI Human endokine alpha and methods of use

IN Yu, Guo-Liang, Berkeley, CA, UNITED STATES

Ni, Jian, Rockville, MD, UNITED STATES

Rosen, Craig A., Laytonsville, MD, UNITED STATES

PA Human Genome Sciences, Inc. (U.S. corporation)

PI US 2002168729 A1 20021114

AI US 2002-136511 A1 20020502 (10)

RLI Division of Ser. No. US 2000-513584, filed on 25 Feb 2000, GRANTED, Pat. No. US 6406867 Division of Ser. No. US 1999-345790, filed on 1 Jul 1999, PENDING Division of Ser. No. US 1997-912227, filed on 15 Aug 1997, GRANTED, Pat. No. US 5998171

PRAI US 1999-136788P 19990528 (60)

US 1999-122099P 19990226 (60)  
 US 1996-24058P 19960816 (60)  
 DT Utility  
 FS APPLICATION  
 LREP STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C., 1100 NEW YORK AVENUE, N.W.,  
 SUITE 600, WASHINGTON, DC, 20005-3934  
 CLMN Number of Claims: 20  
 ECL Exemplary Claim: 1  
 DRWN 4 Drawing Page(s)  
 LN.CNT 9011  
 AB The present invention concerns a novel member of the tumor necrosis  
 factor (TNF) family of cytokines. In particular, isolated nucleic acid  
 molecules are provided encoding the endokine alpha protein. Endokine  
 alpha polypeptides are also provided, as are vectors, host cells and  
 recombinant methods for producing the same. Also provided are diagnostic  
 and therapeutic methods concerning TNF family-related disorders.

L9 ANSWER 8 OF 221 USPATFULL  
 AN 2002:301167 USPATFULL  
 TI Nucleic acids, proteins, and antibodies  
 IN Rosen, Craig A., Laytonsville, MD, UNITED STATES  
 Ruben, Steven M., Olney, MD, UNITED STATES  
 Barash, Steven C., Rockville, MD, UNITED STATES  
 PI US 2002168711 A1 20021114  
 AI US 2001-764868 A1 20010117 (9)  
 PRAI US 2000-179065P 20000131 (60)  
 US 2000-180628P 20000204 (60)  
 US 2000-214886P 20000628 (60)  
 US 2000-217487P 20000711 (60)  
 US 2000-225758P 20000814 (60)  
 US 2000-220963P 20000726 (60)  
 US 2000-217496P 20000711 (60)  
 US 2000-225447P 20000814 (60)  
 US 2000-218290P 20000714 (60)  
 US 2000-225757P 20000814 (60)  
 US 2000-226868P 20000822 (60)  
 US 2000-216647P 20000707 (60)  
 US 2000-225267P 20000814 (60)  
 US 2000-216880P 20000707 (60)  
 US 2000-225270P 20000814 (60)  
 US 2000-251869P 20001208 (60)  
 US 2000-235834P 20000927 (60)  
 US 2000-234274P 20000921 (60)  
 US 2000-234223P 20000921 (60)  
 US 2000-228924P 20000830 (60)  
 US 2000-224518P 20000814 (60)  
 US 2000-236369P 20000929 (60)  
 US 2000-224519P 20000814 (60)  
 US 2000-220964P 20000726 (60)  
 US 2000-241809P 20001020 (60)  
 US 2000-249299P 20001117 (60)  
 US 2000-236327P 20000929 (60)  
 US 2000-241785P 20001020 (60)  
 US 2000-244617P 20001101 (60)  
 US 2000-225268P 20000814 (60)  
 US 2000-236368P 20000929 (60)  
 US 2000-251856P 20001208 (60)  
 US 2000-251868P 20001208 (60)  
 US 2000-229344P 20000901 (60)  
 US 2000-234997P 20000925 (60)  
 US 2000-229343P 20000901 (60)  
 US 2000-229345P 20000901 (60)  
 US 2000-229287P 20000901 (60)

US 2000-229513P 20000905 (60)  
US 2000-231413P 20000908 (60)  
US 2000-229509P 20000905 (60)  
US 2000-236367P 20000929 (60)  
US 2000-237039P 20001002 (60)  
US 2000-237038P 20001002 (60)  
US 2000-236370P 20000929 (60)  
US 2000-236802P 20001002 (60)  
US 2000-237037P 20001002 (60)  
US 2000-237040P 20001002 (60)  
US 2000-240960P 20001020 (60)  
US 2000-239935P 20001013 (60)

DT Utility  
FS APPLICATION  
LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850  
CLMN Number of Claims: 24  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 31967

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, **treating**, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 9 OF 221 USPATFULL  
AN 2002:300827 USPATFULL  
TI Methods and compositions for **treating** secondary tissue damage and other inflammatory conditions and disorders  
IN McDonald, John R., Calgary, AB, UNITED STATES  
Coggins, Philip J., Calgary, AB, UNITED STATES  
PI US 2002168370 A1 20021114  
AI US 2001-792793 A1 20010222 (9)  
RLI Division of Ser. No. US 1999-453851, filed on 2 Dec 1999, PENDING  
Division of Ser. No. US 1999-360242, filed on 22 Jul 1999, PENDING  
Continuation of Ser. No. US 1998-120523, filed on 22 Jul 1998, ABANDONED  
PRAI WO 1999-CA659 19990721  
US 1998-155186P 19980722 (60)  
DT Utility  
FS APPLICATION  
LREP STEPHANIE L. SEIDMAN, ESQ., Heller Ehrman White & McAuliffe, 6th Floor, 4350 La Jolla Village Drive, San Diego, CA, 92122-1246  
CLMN Number of Claims: 24  
ECL Exemplary Claim: 1  
DRWN 5 Drawing Page(s)  
LN.CNT 7972  
AB Nucleic acid molecules that encode conjugates containing as a ligand a chemokine receptor targeting agents, such as chemokines, and a targeted agent, such as a toxin are provided. These conjugates are used to **treat** inflammatory responses associated with activation, proliferation and migration of immune effector cells, including leukocyte cell types, neutrophils, macrophages, and eosinophils.

L9 ANSWER 10 OF 221 USPATFULL  
 AN 2002:300817 USPATFULL  
 TI Methods of preventing or **treating** inflammatory or autoimmune disorders by administering integrin alphanubeta3 antagonists in combination with other prophylactic or therapeutic agents  
 IN Dingivan, Christine, Germantown, MD, UNITED STATES  
 Wilder, Ronald, Rockville, MD, UNITED STATES  
 PI US 2002168360 A1 20021114  
 AI US 2002-91236 A1 20020304 (10)  
 PRAI US 2001-273098P 20010302 (60)  
 US 2001-316321P 20010831 (60)  
 US 2001-346918P 20011019 (60)  
 US 2002-358424P 20020219 (60)  
 DT Utility  
 FS APPLICATION  
 LREP PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711  
 CLMN Number of Claims: 70  
 ECL Exemplary Claim: 1  
 DRWN 2 Drawing Page(s)  
 LN.CNT 8166  
 AB The present invention provides to methods of preventing, **treating** or ameliorating one or more symptoms associated with an autoimmune or inflammatory disorder utilizing combinatorial therapy. In particular, the present invention provides methods of preventing, **treating**, or ameliorating one or more symptoms associated with an autoimmune or inflammatory disorder comprising administering to a subject in need thereof one or more integrin .alpha..sub.V.beta..sub.3 antagonists and at least one other prophylactic or therapeutic agent. The present invention also provides compositions and articles of manufacture for use in preventing, **treating** or ameliorating one or more symptoms associated with an autoimmune or inflammatory disorder.

L9 ANSWER 11 OF 221 USPATFULL  
 AN 2002:300816 USPATFULL  
 TI Human tumor necrosis factor receptor TR9  
 IN Ni, Jian, Germantown, MD, UNITED STATES  
 Yu, Guo-Liang, Berkeley, CA, UNITED STATES  
 Fan, Ping, Potomac, MD, UNITED STATES  
 Gentz, Reiner L., Rockville, MD, UNITED STATES  
 PA Human Genome Sciences, Inc., Rockville, MD, UNITED STATES, 20850 (U.S. corporation)  
 PI US 2002168359 A1 20021114  
 AI US 2002-41574 A1 20020110 (10)  
 RLI Division of Ser. No. US 2000-527236, filed on 16 Mar 2000, PATENTED  
 Continuation-in-part of Ser. No. US 1998-95094, filed on 10 Jun 1998, PENDING  
 PRAI US 1999-134220P 19990514 (60)  
 US 1999-126019P 19990324 (60)  
 US 1997-52991P 19970611 (60)  
 DT Utility  
 FS APPLICATION  
 LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850  
 CLMN Number of Claims: 24  
 ECL Exemplary Claim: 1  
 DRWN 11 Drawing Page(s)  
 LN.CNT 9755  
 AB The present invention relates to a novel member of the tumor necrosis factor family of receptors. In particular, isolated nucleic acid molecules are provided encoding the human TR9 receptor. TR9 polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods

for identifying agonists and antagonists of TR9 receptor activity.

L9 ANSWER 12 OF 221 USPATFULL  
AN 2002:300801 USPATFULL  
TI Sensitization of chemotherapeutic agent resistant neoplastic cells with a virus  
IN Coffey, Matthew C., Calgary, CANADA  
Thompson, Bradley G., Calgary, CANADA  
PA Oncolytics Biotech, Inc., Calgary, AB, CANADA, T2N 1X7 (non-U.S. corporation)  
PI US 2002168344 A1 20021114  
AI US 2002-76074 A1 20020215 (10)  
PRAI US 2001-270363P 20010220 (60)  
DT Utility  
FS APPLICATION  
LREP BURNS DOANE SWECKER & MATHIS L L P, POST OFFICE BOX 1404, ALEXANDRIA, VA, 22313-1404  
CLMN Number of Claims: 34  
ECL Exemplary Claim: 1  
DRWN 1 Drawing Page(s)  
LN.CNT 1036  
AB The present invention relates to a method of increasing the sensitivity of neoplastic cells to chemotherapeutic agents by using a virus, a method of **treating** proliferative disorders with a virus and chemotherapeutic agents, and a method for preventing a neoplasm from developing drug resistance to chemotherapeutic agents. The virus is preferably a reovirus.

L9 ANSWER 13 OF 221 USPATFULL  
AN 2002:295172 USPATFULL  
TI Materials and methods to potentiate cancer **treatment**  
IN Halbrook, James, Woodinville, WA, UNITED STATES  
Kesicki, Edward A., Bothell, WA, UNITED STATES  
Burgess, Laurence E., Boulder, CO, UNITED STATES  
Schlachter, Stephen T., Boulder, CO, UNITED STATES  
Eary, Charles T., Longmont, CO, UNITED STATES  
Schiro, Justin G, Firestone, CO, UNITED STATES  
Huang, Hongmei, Broomfield, CO, UNITED STATES  
Evans, Michael, Louisville, CO, UNITED STATES  
Han, Yongxin, Longmont, CO, UNITED STATES  
PI US 2002165218 A1 20021107  
AI US 2001-941897 A1 20010828 (9)  
PRAI US 2000-229899P 20000901 (60)  
DT Utility  
FS APPLICATION  
LREP MARSHALL, GERSTEIN & BORUN, 6300 SEARS TOWER, 233 SOUTH WACKER, CHICAGO, IL, 60606-6357  
CLMN Number of Claims: 37  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 5685  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB Compounds that inhibit DNA-dependent protein kinase, compositions comprising the compounds, methods to inhibit the DNA-PK biological activity, methods to sensitize cells the agents that cause DNA lesions, and methods to potentiate cancer **treatment** are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L9 ANSWER 14 OF 221 USPATFULL  
AN 2002:295092 USPATFULL  
TI Nucleic acids, proteins, and antibodies

IN Ruben, Steven M., Olney, MD, UNITED STATES  
Barash, Steven C., Rockville, MD, UNITED STATES  
Rosen, Craig A., Laytonsville, MD, UNITED STATES  
Birse, Charles E., North Potomac, MD, UNITED STATES

PA Human Genome Sciences, Inc., Rockville, MD, UNITED STATES, 20850 (U.S. corporation)

PI US 2002165137 A1 20021107

AI US 2001-860670 A1 20010521 (9)

RLI Continuation-in-part of Ser. No. WO 2001-US1346, filed on 17 Jan 2001, UNKNOWN Continuation-in-part of Ser. No. US 2001-764859, filed on 17 Jan 2001, PENDING

PRAI US 2000-205515P 20000519 (60)  
US 2000-179065P 20000131 (60)  
US 2000-180628P 20000204 (60)  
US 2000-225447P 20000814 (60)  
US 2000-218290P 20000714 (60)  
US 2000-216880P 20000707 (60)  
US 2000-234997P 20000925 (60)  
US 2000-229343P 20000901 (60)  
US 2000-236367P 20000929 (60)  
US 2000-239937P 20001013 (60)  
US 2000-249210P 20001117 (60)  
US 2000-249211P 20001117 (60)  
US 2000-249214P 20001117 (60)  
US 2000-231243P 20000908 (60)  
US 2000-246477P 20001108 (60)  
US 2000-246528P 20001108 (60)  
US 2000-246525P 20001108 (60)  
US 2000-246476P 20001108 (60)  
US 2000-246526P 20001108 (60)  
US 2000-249265P 20001117 (60)  
US 2000-230437P 20000906 (60)  
US 2000-251990P 20001208 (60)  
US 2000-251988P 20001205 (60)  
US 2000-251030P 20001205 (60)  
US 2000-251479P 20001206 (60)  
US 2000-256719P 20001205 (60)  
US 2000-250160P 20001201 (60)  
US 2000-251989P 20001208 (60)  
US 2000-250391P 20001201 (60)  
US 2000-254097P 20001211 (60)  
US 2000-179065P 20000131 (60)  
US 2000-180628P 20000204 (60)  
US 2000-214886P 20000628 (60)  
US 2000-217487P 20000711 (60)  
US 2000-225758P 20000814 (60)  
US 2000-220963P 20000726 (60)  
US 2000-217496P 20000711 (60)  
US 2000-225447P 20000814 (60)  
US 2000-218290P 20000714 (60)  
US 2000-225757P 20000814 (60)  
US 2000-226868P 20000822 (60)  
US 2000-216647P 20000707 (60)  
US 2000-225267P 20000814 (60)  
US 2000-216880P 20000707 (60)  
US 2000-225270P 20000814 (60)  
US 2000-251869P 20001208 (60)  
US 2000-235834P 20000927 (60)  
US 2000-234274P 20000921 (60)

DT Utility

FS APPLICATION

LREP HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

antitumor effects, compared to 131I-mAb A33 alone or either drug regimen alone. 5-FU was administered either at 30 mg/kg/day for 5 days or at 75 mg/kg/day on days 1 and 5. In assessing the reduction in tumor volumes over the first 28 days of the experiment, 5-FU treatment (with or without leucovorin) in combination with 131I-mAb A33 showed a statistically significant additive antitumor effect compared to 131I-mAb A33 alone or to chemotherapy alone. When long-term survival was used as an end point, 38% of the mice treated with 5-FU and 131I-mAb A33 were disease free at 276 days compared to none from any other group, suggesting a **synergistic** effect. These data indicate that Phase II clinical trials combining radiolabeled antibody therapy with 5-FU-based treatments are warranted.

L6 ANSWER 13 OF 22 CANCERLIT  
 AN 97223915 CANCERLIT  
 DN 97223915 PubMed ID: 9070496  
 TI **Doxorubicin** sensitizes human bladder carcinoma cells to Fas-mediated cytotoxicity.  
 AU Mizutani Y; Okada Y; Yoshida O; Fukumoto M; Bonavida B  
 CS Department of Urology, Faculty of Medicine, Kyoto University, Japan.  
 SO CANCER, (1997 Mar 15) 79 (6) 1180-9.  
 Journal code: 0374236. ISSN: 0008-543X.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS MEDLINE; Abridged Index Medicus Journals; Priority Journals  
 OS MEDLINE 97223915  
 EM 199704  
 ED Entered STN: 19970509  
 Last Updated on STN: 19970509  
 AB BACKGROUND: The resistance of bladder carcinoma to anticancer chemotherapeutic agents remains a major problem. Hence, several immunotherapeutic approaches have been developed to treat the drug-resistant cancer cells. Fas antigen (Fas) and Fas ligand participate in cytotoxicity mediated by T lymphocytes and natural killer cells. Like Fas ligand, anti-Fas monoclonal antibody (MoAb) induces apoptosis of the cells expressing Fas. This study examined whether bladder carcinoma cells are sensitive to cytotoxicity mediated by anti-Fas MoAb and whether anticancer agents **synergize** with anti-Fas MoAb in cytotoxicity. METHODS: Cytotoxicity was determined by a 1-day microculture tetrazolium dye assay. **Synergy** was assessed by isobolographic analysis. RESULTS: The T24 human bladder carcinoma cell line constitutively expressed the Fas on the cell surface; however, T24 line was resistant to anti-Fas MoAb. Treatment of T24 cells with anti-Fas MoAb in combination with mitomycin C, methotrexate, or 5-**fluorouracil** did not overcome their resistance to these agents. However, treatment of T24 cells with a combination of anti-Fas MoAb and **doxorubicin** resulted in a **synergistic** cytotoxic effect. In addition, the **doxorubicin**-resistant T24 cells were sensitive to treatment with a combination of anti-Fas MoAb and **doxorubicin**. **Synergy** was also achieved in three other bladder carcinoma cell lines and four freshly derived human bladder carcinoma cells. Treatment with anti-Fas MoAb in combination with epirubicin or pirarubicin also resulted in a **synergistic** cytotoxic effect on T24 cells. The mechanisms of **synergy** were examined. Anti-Fas MoAb did not affect the intracellular accumulation of **doxorubicin**, the expression of P-glycoprotein, or the expression of the antioxidant glutathione S-transferase-pi mRNA. However, treatment with **doxorubicin** enhanced the expression of Fas on T24 cells. CONCLUSIONS: This study demonstrated that treatment of bladder carcinoma cells with **doxorubicin** sensitized the cells to lysis by anti-Fas MoAb. The **synergistic** effect obtained with established **doxorubicin**-resistant bladder carcinoma cells and freshly isolated bladder carcinoma cells suggests that drug-resistant bladder carcinoma cells can be



sensitized by **doxorubicin** to Fas- and Fas ligant-mediated cytotoxicity by lymphocytes. Furthermore, the sensitization required low concentrations of **doxorubicin**, thus supporting the in vivo application of a combination of chemotherapy and immunotherapy in the treatment of drug-resistant and/or immunotherapy-resistant bladder carcinoma.

L6 ANSWER 14 OF 22 CANCERLIT  
AN 97205972 CANCERLIT  
DN 97205972 PubMed ID: 9157070  
TI Effects of 13-hydroxy SM5887 in combination with other anticancer agents on human tumor cell lines.  
AU Takagi T; Yazawa Y; Suzuki K; Yamauchi Y; Kano Y  
CS Division of Orthopedic Oncology, Tochigi Cancer Center, Japan.  
SO INVESTIGATIONAL NEW DRUGS, (1996) 14 (4) 357-63.  
Journal code: 8309330. ISSN: 0167-6997.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS MEDLINE; Priority Journals  
OS MEDLINE 97205972  
EM 199705  
ED Entered STN: 19970618  
Last Updated on STN: 19970618  
AB A new **anthracycline** derivative, SM5887, in combination with commonly used anticancer agents was evaluated against T-cell leukemia MOLT-3 and human osteosarcoma MG-63 cell lines in culture. MOLT-3 and MG-63 cells were incubated with various concentrations of 13-hydroxy SM5887 (SM5887-OH, the active metabolite of SM5887) and other drugs for 3 and 4 days, respectively. Cell growth inhibition was determined by MTT assay. The antitumor effects of the drug combinations at 80% inhibitory concentration (IC80) were analyzed by the isobologram of Steel and Peckham. In MOLT-3 cells, SM5887-OH had additive effects with bleomycin, etoposide, **doxorubicin**, cisplatin, mitomycin-C, 4-hydroperoxy ifosfamide, 5-**fluorouracil**, cytarabine, and vincristine, whereas it had mainly protective (marked antagonistic) effects with methotrexate. In MG-63 cells, SM5887-OH had additive effects with bleomycin, etoposide, **doxorubicin**, cisplatin, mitomycin-C, 4-hydroperoxy ifosfamide; mainly subadditive (mild antagonistic) effects with 5-**fluorouracil** and cytarabine; and mainly protective (marked antagonistic) effects with vincristine and methotrexate. These findings suggest that SM5887 is suitable for simultaneous administration with bleomycin, etoposide, **doxorubicin**, cisplatin, mitomycin-C, or ifosfamide and not suitable for simultaneous administration with methotrexate. The effects of SM5887 in combination with 5-**fluorouracil**, cytarabine or vincristine may be variable, depending on cell lines. To find optimal combinations, further in vitro and in vivo studies of antitumor activity and toxicity appear to be warranted.

L6 ANSWER 15 OF 22 CANCERLIT  
AN 97049170 CANCERLIT  
DN 97049170 PubMed ID: 8893900  
TI Paclitaxel combination therapy in the treatment of metastatic breast cancer: a review.  
AU Holmes F A  
CS Department of Breast Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston 77030-4009, USA.  
SO SEMINARS IN ONCOLOGY, (1996 Oct) 23 (5 Suppl 11) 46-56. Ref: 55  
Journal code: 0420432. ISSN: 0093-7754.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LA English

FS MEDLINE; Priority Journals  
 OS MEDLINE 97049170  
 EM 199612  
 ED Entered STN: 19970108  
 Last Updated on STN: 19970108  
 AB Combinations of active antineoplastic agents have been the most effective treatment for metastatic breast cancer. Criteria for an effective combination include use of drugs with different mechanisms of action, nonoverlapping toxic effects, and **synergistic**, or at least additive, antitumor activity. Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ), with its unique mechanism of action, offers an excellent opportunity for development of effective combination therapy against breast cancer. However, a number of problems have hindered the rapid development of effective combinations. The most obvious problem is the lack of a defined optimal dose and schedule of administration. The second problem has been the demonstration of unexpected interactions between paclitaxel and the other component(s) of the combination, often resulting in unusual and serious toxic effects. This review will focus on the phase I and II trials of paclitaxel in combination with established antineoplastic drugs (except **doxorubicin** and congeners, which is covered elsewhere in this issue) for breast cancer: cisplatin, 5-**fluorouracil** with or without folinic acid, cyclophosphamide, radiation therapy, as well as novel investigational agents or strategies, edatrexate, monoclonal antibodies to oncogenes, growth factors, and gene therapy with insertion of multidrug resistance gene into blood stem cells. Combination therapy offers exciting possibilities of enhanced antitumor efficacy. However, given the unexpected and serious toxic effects observed, only proven combinations should be used outside the context of a clinical trial. Additionally, the burden of proof will be to show that these combinations have increased antitumor activity, decreased toxicity, or both compared with single-agent paclitaxel.

L6 ANSWER 16 OF 22      CANCERLIT  
 AN 96709293      CANCERLIT  
 DN 96709293  
 TI New chemotherapeutic agents for breast cancer (Meeting abstract).  
 AU Gianni L  
 CS Istituto Nazionale Tumori, Milan, Italy.  
 SO Non-serial, (1995) Perspectives in Breast Cancer, September 29-30, 1995, Phoenix, Arizona, p. 33-4, 1995. .  
 DT (MEETING ABSTRACTS)  
 (CLINICAL TRIAL)  
 (RANDOMIZED CONTROLLED TRIAL)  
 LA English  
 FS Institute for Cell and Developmental Biology  
 EM 199610  
 ED Entered STN: 19970509  
 Last Updated on STN: 19970509  
 AB Breast cancer remains a major cause of death and morbidity among women despite significant survival advantage and substantial palliation provided by chemotherapies-based on cyclophosphamide, antimetabolites and **anthracyclines** (eg CMF and FAC). New compounds active on microtubules (taxanes and vinorelbine), synthetic analogs of **anthracyclines** (anthrapyrazoles), and antimetabolites endowed with more selective and better mechanisms of action (edatrexate, inhibitors of thymidylate synthase) are recently undergoing evaluation in metastatic breast cancer, and are attracting special interest. The taxanes paclitaxel (PCT) and docetaxel (DCT) share the novel mechanism of stabilizing microtubules and promoting their assembly. Both drugs require premedication with corticosteroids and antihistamines to prevent severe hypersensitivity reactions, and cause dose-limiting neutropenia. PCT also causes peripheral neuropathy, while DCT can cause unpredictable and severe skin toxicity and edema and effusions due to a capillary leak syndrome. Single agent PCT was very active in multiple Phase II trials in patients

with various numbers and types of prior chemotherapy and different disease extent (20-60% CR plus PR). Due to threshold pharmacodynamics and nonlinear pharmacokinetics, tolerability of PCT is schedule-dependent. Effective doses ranged from 135 to 250 mg/m<sup>2</sup>. Activity was observed with all infusion schedules (1, 3 and 24 hr) and in women with **anthracycline**-resistant tumors (25-38%). Since PCT is cell-specific and long exposures overcome multidrug resistance, a 96 hr infusion schedule was implemented and found very active in **anthracycline**-refractory patients (48%), and active in women who failed short infusion taxanes. Even though the optimal dose and schedule are still undefined, available data on efficacy supported the introduction of PCT after standard adjuvant chemotherapy, and the evaluation of its use in combination with **doxorubicin**, cyclophosphamide, cisplatin, **fluorouracil** plus leucovorin and edatrexate. The tolerability of combinations with PCT depends on the sequence of administration of the taxane and the combined drug except when a short infusion is adopted. In all combinations PCT is active and well tolerated. Very promising efficacy was observed for PCT with 3 hr and bolus **doxorubicin** (DOX), about 40% CR and 50% PR, in two Phase II studies that also showed a high incidence of clinically reversible congestive heart failure (14-18%). Since efficacy is lower and cardiac toxicity is minimal when PCT is given by longer infusion with DOX, the effects of schedule on the potential therapeutic and toxic **synergy** require further investigation. DCT also displays very good efficacy in breast cancer, with about 70% major responses in untreated patients, and more than 50% in **anthracycline**-resistant tumors. Efficacy and tolerability are not schedule-dependent. At recommended doses (100 or 75 mg/m<sup>2</sup> in 1 hr q3wk) the capillary leak syndrome may affect quality of life and its common onset after multiple cycles may limit the use of DCT for palliation in metastatic breast cancer. Combinations with **anthracyclines** are now being evaluated, but results are not yet available. Vinorelbine (VNB) was developed because of its lower neurotoxic potential compared to other vinca alkaloids. It causes transient neutropenia and mild constipation and fatigue as most common toxicities. It can be given by weekly administration (20-30 mg/m<sup>2</sup>/wk), and is active by the oral route. VNB has major activity in metastatic breast cancer (30-40% responses in pretreated and 45-60% in untreated women). It can be combined at nearly full doses with DOX as first line chemotherapy (21% CR and 53% PR), while in combination with daily x5 **fluorouracil** it is active in about 60% of pretreated patients. Among the anthracyclines, piroxantrone had minor activity and was disappointingly cardiotoxic. The future development of losoxantrone, that was active in 60% of patients with minimal prior chemotherapy, depends on the clinical demonstration of its expected low toxicity (ABSTRACT TRUNCATED)

L6 ANSWER 17 OF 22      CANCERLIT  
AN 96273138      CANCERLIT  
DN 96273138      PubMed ID: 8702227  
TI Antitumor activity of menogaril alone, and in combination against human mammary cancer models in mice and rats.  
AU Yoshida M; Fujioka A; Nakano K; Kobunai T; Saito H; Toko T; Takeda S; Unemi N  
CS Anticancer and Antimicrobials Research Laboratory, Taiho Pharmaceutical Co., Ltd., Tokushima, Japan.  
SO ANTICANCER RESEARCH, (1996 May-Jun) 16 (3A) 1155-9.  
Journal code: 8102988. ISSN: 0250-7005.  
CY Greece  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS MEDLINE; Priority Journals  
OS MEDLINE 96273138  
EM 199608  
ED Entered STN: 19961008  
Last Updated on STN: 19970509

AB Menogaril is an antitumor agent different from other **anthracyclines** in being active after oral administration. To predict its clinical effectiveness by this route against human breast cancer, we compared its antitumor activity against breast cancer in experimental animals with that of injected Adriamycin. Menogaril had half the much antitumor activity of Adriamycin against human mammary cancer cell lines. Menogaril given orally also had a antitumor activity against mammary cancer caused by 7,12-dimethyl-benz[a]anthracene in rats comparable with that of Adriamycin. The high concentration of menogaril in tumor tissue seemed to contribute to its effectiveness. Of several combinations of cyclophosphamide, Adriamycin, menogaril, and 5-**fluorouracil**, the combination of cyclophosphamide, menogaril, and 5-**fluorouracil** was most effective against mouse leukemia L1210 and human breast cancer xenografts in mice. This combination might have antitumor activity against breast cancer superior to that of the therapy currently of first choice (cyclophosphamide, Adriamycin, and 5-**fluorouracil**) in the clinic.

L6 ANSWER 18 OF 22 CANCERLIT

AN 96169517 CANCERLIT

DN 96169517 PubMed ID: 8669796

TI [Chemotherapy and cardiotoxicity].  
Chimiotherapie et cardiotoxicite.

AU Brestescher C; Pautier P; Farge D

CS Service de Medecine Interne et Pathologie Vasculaire, Hopital Saint-Louis, Paris.

SO ANNALES DE CARDIOLOGIE ET D ANGEIOLOGIE, (1995 Oct) 44 (8) 443-7.  
Journal code: 0142167. ISSN: 0003-3928.

CY France

DT Journal; Article; (JOURNAL ARTICLE)

LA French

FS MEDLINE; Priority Journals

OS MEDLINE 96169517

EM 199608

ED Entered STN: 19960911

Last Updated on STN: 19960911

AB Among the various anticancer drugs, used alone or in combination during courses of chemotherapy, **anthracyclines** (leader: **doxorubicin**) are responsible for direct myocardial toxicity, which can exceptionally be acute, but more often chronic with a delayed onset. This cardiotoxicity is directly proportional to the cumulative dose administered and the recommended total dose for **doxorubicin** is 550 mg/m<sup>2</sup>. The risk factors able to potentiate cardiotoxicity must be analysed before starting chemotherapy and follow-up by ultrasonography and/or isotope ejection fraction must be repeated before each course. The treatment of **anthracycline**-induced heart failure consists of digitalis alkaloids combined with angiotensin converting enzyme inhibitors. The cardiac toxicity of 5FU is currently explained by the theory of coronary spasm, based on clinical findings such as chest pain associated with ischaemic electrical modifications. The incidence of this toxicity is low, but it can be fatal. Exceptional examples include the cardiotoxicity induced by high-dose cyclophosphamide responsible for acute haemorrhagic myocarditis, potentiation of the cardiotoxic effect of **anthracyclines** by dacarbazine and plicamycin, and serious ventricular and supraventricular arrhythmias induced by amsacrine. Among the various cytokines used in oncology, interferon is responsible for heart failure, reversible after stopping treatment, but also for ventricular arrhythmias, or even sudden death, the pathophysiology of which still remains unclear.

L6 ANSWER 19 OF 22 CANCERLIT

AN 90381585 CANCERLIT

DN 90381585 PubMed ID: 2119245

TI Modulation of the effect of **anthracycline** efficacy and toxicity

by ICRF-187.

AU Blum R H; Walsh C; Green M D; Speyer J L  
CS Division of Medical Oncology, Kaplan Cancer Center, New York University  
Medical Center, New York 10016.  
NC CA 16087 (NCI)  
R01 CA 36524 (NCI)  
SO CANCER INVESTIGATION, (1990) 8 (2) 267-8.  
Journal code: 8307154. ISSN: 0735-7907.  
CY United States  
DT (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
(RANDOMIZED CONTROLLED TRIAL)  
LA English  
FS MEDLINE; Priority Journals  
OS MEDLINE 90381585  
EM 199010  
ED Entered STN: 19941107  
Last Updated on STN: 19941107

L6 ANSWER 20 OF 22 CANCERLIT  
AN 85016694 CANCERLIT  
DN 85016694 PubMed ID: 6484579  
TI Biologic and biochemical effects of mitoxantrone.  
AU Durr F E  
SO SEMINARS IN ONCOLOGY, (1984 Sep) 11 (3 Suppl 1) 3-10.  
Journal code: 0420432. ISSN: 0093-7754.

CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS MEDLINE; Priority Journals  
OS MEDLINE 85016694  
EM 198411  
ED Entered STN: 19941107  
Last Updated on STN: 19941107

AB Mitoxantrone (1,4-dihydroxy-5,8-bis[(2-[(2-hydroxyethyl)-amino]-ethyl)amino]-9,10-anthracenedione dihydrochloride) is a representative of a new class of chemical compounds with antineoplastic activity. It was one of a number of polycyclic aromatic compounds tested at the American Cyanamid Laboratories and was the most effective and potent derivative synthesized. Mitoxantrone produced significant increases in life span and long-term survivors when tested against P388 and L1210 leukemias, B16 melanoma, and colon tumor 26 transplanted into mice. In comparative animal trials, it proved more effective than most of the other agents tested, including **doxorubicin**, cyclophosphamide, methotrexate, cytarabine, and 5-**fluorouracil**. It was also active against intravenously implanted L1210 leukemia, in contrast to **doxorubicin**, though this is considered to have a similar mode of action. Mitoxantrone also demonstrated moderate activity against sublines of the mouse leukemias, which were resistant to **anthracyclines**. Significant therapeutic **synergism** against P388 leukemia was observed when mitoxantrone was administered on the same day as methotrexate and cytarabine or in sequence with cyclophosphamide, cisplatin, or vincristine sulfate. Mitoxantrone is active intraperitoneally, intramuscularly, subcutaneously, and intravenously, but oral activity has not been demonstrated. Although dose schedule did not appear critical, treatment every 4 days X 3 appeared to be the most effective. The mechanism of action of mitoxantrone has not been fully elucidated, but it is known to inhibit DNA and RNA synthesis. In cell culture, mitoxantrone induces nuclear aberrations with chromosomal scattering and morphologic alterations similar to those induced by **doxorubicin**. Drug-induced cell kill was not phase specific. Experiments with a resistant human colon carcinoma cell line (WiDr) indicated that resistance may be due to alterations of the cell membrane with decreased uptake. Mitoxantrone has markedly less cardiotoxicity than **doxorubicin**, and this may be linked to the fact that the drug does

not induce free radical formation but inhibits lipid peroxidation.

L6 ANSWER 21 OF 22       CANCERLIT  
AN 80806064       CANCERLIT  
DN 80806064  
TI NEW DEVELOPMENTS ON THE MECHANISMS OF ACTION OF ANTINEOPLASTIC DRUGS.  
AU Donehower R C; Myers C E; Chabner B A  
CS Clinical Pharmacology Branch, NCI, NIH, Bethesda, MD, 20014.  
SO Life Sci, (1979) 25 (1) 1-13.  
ISSN: 0024-3205.  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Hierarchical Classification of Proteins  
EM 198001  
ED Entered STN: 19941107  
Last Updated on STN: 19941107  
AB Studies on the mode of action of **anthracyclines**, bleomycin (BL), methotrexate (MTX), and **fluoropyrimidines** are reviewed. Experiments with the **anthracycline doxorubicin** (DOX) have shown that enzymatic mechanisms exist for reducing DOX to a free radical which is capable of generating toxic oxygen radicals. However, no clear relationship has been established between the presence of these radical generating systems and tumor response. Studies of BL, an antitumor agent which produces DNA strand breakage, have led to the proposal of a mechanism whereby the spontaneous oxidation of BL-bound Fe(II) to Fe(III) produces free radical species which attack adjacent DNA. In vitro studies have shown that free radicals or reducing compounds promote the reaction of the Fe(II)-BL complex with DNA, suggesting that BL in combination with free radical producing modalities such as ionizing radiation might have a **synergistic** effect. However, inconsistent results have been generated from studies of BL-radiation interaction in tissue culture, and several clinical trials of concurrent BL and radiation have resulted in an unexpected degree of pulmonary toxicity. Therapeutic **synergism** has been demonstrated between MTX and 5-**fluorouracil** (5-FU); the optimal schedule for this **synergism** is MTX administration at least 1 hr before 5-FU administration. The superiority of this sequence of drug administration may be due to minimizing 5-FU antagonism of the antipurine effects of MTX or to increased 5-FU activation. Varying responses to combinations of MTX and 5-FU have been observed due to biological differences among the various mammalian cell lines studied. (84 Refs)

L6 ANSWER 22 OF 22       CANCERLIT  
AN 79803347       CANCERLIT  
DN 79803347  
TI CARDIAC RESPONSE TO COMBINED MODALITY THERAPY.  
AU Eltringham J R  
CS Dept. Radiology, Div. Radiation Therapy, Univ. Utah Medical Center, Salt Lake City, UT, 84132.  
SO Front Radiat Ther Oncol, (1979) 13 161-174.  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Hierarchical Classification of Proteins  
EM 197907  
ED Entered STN: 19941107  
Last Updated on STN: 19941107  
AB Human cardiotoxicity resulting from combined modality therapy is discussed. It has been well documented that ionizing radiation in the therapeutic-dose range is capable of damaging the human heart. This cardiotoxicity may be enhanced by the addition of the **anthracycline** compounds, especially adriamycin (ADR). The incidence of ADR cardiomyopathy is related to the total cumulative dose received, and cases of congestive heart failure and/or cardiomyopathy have been reported at cumulative doses lower than the max recommended dose of

550 mg/m2. Whether the enhanced heart damage of combined ADR and radiation treatment is due to additive or **synergistic** effects has not been definitively established, although preliminary results suggest that in the rabbit the effects may be accounted for by the independent actions of the two agents. While there have been a small number of reports of cardiotoxicity due to 5-**fluorouracil** or vincristine, generally the cause of drug-induced cardiotoxicity in many case reports is adriamycin. The possibility exists that other chemotherapeutic agents, especially the antitumor antibiotics, are capable of enhancing ADR cardiotoxicity. With the delayed and progressive nature of the cardiomyopathy seen with ADR, unanticipated relatively long-term cardiotoxicity may yet be seen with other agents in combination with radiation. Rubidazone may possess a high degree of activity, with less cardiotoxicity than ADR or **daunorubicin**. (46 Refs)

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=> s 14 and (gemcitabine or fluoropyrimidine or fluorouracil or cytidine)

6423 ANTHRACYCLINE

2494 ANTHRACYCLINES

7535 ANTHRACYCLINE

(ANTHRACYCLINE OR ANTHRACYCLINES)

6567 DAUNORUBICIN

3 DAUNORUBICINS

6567 DAUNORUBICIN

(DAUNORUBICIN OR DAUNORUBICINS)

26713 DOXORUBICIN

4 DOXORUBICINS

26713 DOXORUBICIN

(DOXORUBICIN OR DOXORUBICINS)

70879 SYNERG?

1759 GEMCITABINE

456 FLUOROPYRIMIDINE

409 FLUOROPYRIMIDINES

742 FLUOROPYRIMIDINE  
 (FLUOROPYRIMIDINE OR FLUOROPYRIMIDINES)  
 23151 FLUOROURACIL  
 13 FLUOROURACILS  
 23151 FLUOROURACIL  
 (FLUOROURACIL OR FLUOROURACILS)  
 6220 CYTIDINE  
 111 CYTIDINES  
 6281 CYTIDINE  
 (CYTIDINE OR CYTIDINES)  
 L7 18 L4 AND (GEMCITABINE OR FLUOROPYRIMIDINE OR FLUOROURACIL OR CYTIDINE)

=> dis 17 1-18 bib abs

L7 ANSWER 1 OF 18 MEDLINE  
 AN 2002415865 MEDLINE  
 DN 22160464 PubMed ID: 12170449  
 TI Docetaxel in the treatment of breast cancer: an update on recent studies.  
 AU Nabholz Jean-Marc A; Reese David M; Lindsay Mary-Ann; Riva Alessandro  
 CS Cancer Therapy Development Program, Jonsson Comprehensive Cancer Center,  
 University of California, Los Angeles, CA 90095-7077, USA.  
 SO SEMINARS IN ONCOLOGY, (2002 Jun) 29 (3 Suppl 12) 28-34. Ref: 23  
 Journal code: 0420432. ISSN: 0093-7754.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 200208  
 ED Entered STN: 20020810  
 Last Updated on STN: 20020831  
 Entered Medline: 20020830  
 AB Recently there has been great interest in developing combination regimens involving taxanes and **anthracyclines** for the treatment of advanced breast cancer. Docetaxel in particular has substantial activity when combined with **doxorubicin**. In one randomized trial, the combination of **doxorubicin** 50 mg/m<sup>2</sup> and docetaxel 75 mg/m<sup>2</sup> showed significantly greater activity than **doxorubicin** plus cyclophosphamide (AC), producing a higher response rate (60% v 47%) and longer time to progression. In a second study, 484 patients were randomized to receive either docetaxel plus **doxorubicin** and cyclophosphamide (TAC) or 5-fluorouracil plus **doxorubicin** and cyclophosphamide. The response rate was significantly higher in the TAC arm (54% v 42%), including patients with unfavorable prognostic factors. Febrile neutropenia occurred more frequently in patients receiving TAC, but the incidence of infection and septic death was low and no greater than in the 5-fluorouracil/**doxorubicin**/cyclophosphamide arm. TAC was not associated with an increased risk of cardiotoxicity. Data on time to progression and survival are not yet available. The TAC and **doxorubicin**/docetaxel regimens have been compared with non-docetaxel-containing programs in randomized adjuvant trials which have completed accrual but are not yet mature. A second generation of adjuvant trials compares sequential versus synchronous docetaxel-based polychemotherapy. In addition, based on preclinical data suggesting a **synergistic** interaction between docetaxel, platinum salts, and trastuzumab, as well as preliminary data from pilot studies in patients with HER2-positive metastatic disease showing tolerability and activity, adjuvant studies of this novel three-agent combination are in progress in patients with HER2-positive early breast cancer.  
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L7 ANSWER 2 OF 18 MEDLINE



AN 2002109922 MEDLINE  
 DN 21830591 PubMed ID: 11841932  
 TI Future treatment options with capecitabine in solid tumours.  
 AU Wilke H  
 CS Department of Internal Medicine and Oncology/Hematology, Kliniken  
 Essen-Mitte, Germany.. hwilke@kem.telba.de  
 SO EUROPEAN JOURNAL OF CANCER, (2002 Feb) 38 Suppl 2 21-5.  
 Journal code: 9005373. ISSN: 0959-8049.  
 CY England: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 200207  
 ED Entered STN: 20020214  
 Last Updated on STN: 20020716  
 Entered Medline: 20020715  
 AB The oral **fluoropyrimidine**, capecitabine is attracting great  
 interest in the context of tumour-selective therapy and rationally  
 designed combination regimens. Agents such as taxanes upregulate thymidine  
 phosphorylase (TP), and there is therefore a clear rationale for their  
 combination with capecitabine. Preclinical studies of capecitabine/taxane  
 combination therapy demonstrated **synergistic** antitumour activity  
 and phase I studies showed encouraging efficacy. Therefore, a randomised,  
 phase III trial (docetaxel versus docetaxel/capecitabine) has been  
 initiated in **anthracycline**-refractory metastatic breast cancer  
 patients. Recruitment is complete. In colorectal cancer,  
 capecitabine/oxaliplatin combination therapy is promising and a phase I,  
 dose-finding trial has been conducted in patients with refractory  
 metastatic solid tumours. A similar trial has evaluated  
 capecitabine/irinotecan combination treatment. Capecitabine is also being  
 investigated as adjuvant therapy for colorectal and breast cancers. The  
 primary objective of the ongoing X-ACT trial in almost 2000 Dukes' C colon  
 cancer patients is to demonstrate at least equivalent disease-free  
 survival between capecitabine and the Mayo Clinic regimen. In addition,  
 the CALGB is planning a randomised, phase III trial of capecitabine versus  
**doxorubicin**/cyclophosphamide or cyclophosphamide/methotrexate/5-  
**fluorouracil** (CMF) as adjuvant treatment in high-risk,  
 node-negative breast cancer patients aged >65 years.

L7 ANSWER 3 OF 18 MEDLINE  
 AN 2001641940 MEDLINE  
 DN 21551584 PubMed ID: 11694788  
 TI New combinations with Herceptin in metastatic breast cancer.  
 AU Winer E P; Burstein H J  
 CS Dana-Farber Cancer Institute, Boston, Mass 02115, USA..  
 ewiner@partners.org  
 SO ONCOLOGY, (2001) 61 Suppl 2 50-7. Ref: 41  
 Journal code: 0135054. ISSN: 0030-2414.  
 CY Switzerland  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 200112  
 ED Entered STN: 20011107  
 Last Updated on STN: 20020124  
 Entered Medline: 20011228  
 AB Preclinical data indicate that trastuzumab (Herceptin) has the potential  
 for **synergistic** or additive effects in combination with  
 therapies including chemotherapy and hormonal agents, providing the  
 rationale for a number of clinical trials in women with HER2-positive  
 metastatic breast cancer. A recently reported phase II trial has  
 demonstrated that trastuzumab plus vinorelbine is both effective (overall

response rate 75%) and well tolerated, with the major side effects being typical of single-agent vinorelbine. Other combinations of trastuzumab with a variety of other chemotherapeutic and hormonal agents are also being assessed. In an effort to overcome the cardiotoxicity observed with trastuzumab plus **doxorubicin** in the pivotal phase III trial, combination regimens involving potentially less toxic **anthracyclines** such as epirubicin and liposomal formulations of **doxorubicin** are ongoing. In addition, trials are investigating whether trastuzumab can reverse the resistance to hormonal therapy that develops in most women with metastatic breast cancer. These and other studies will identify the regimens that produce the best outcomes with the fewest possible side effects in women with HER2-positive breast cancer.  
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L7 ANSWER 4 OF 18 MEDLINE  
AN 2000499428 MEDLINE  
DN 20496124 PubMed ID: 11043419  
TI Induction of apoptosis using 2',2' difluorodeoxycytidine (gemcitabine) in combination with antimetabolites or **anthracyclines** on malignant lymphatic and myeloid cells. Antagonism or **synergism** depends on incubation schedule and origin of neoplastic cells.  
AU Chow K U; Ries J; Weidmann E; Pourebrahim F; Napieralski S; Stieler M; Boehrer S; Rummel M J; Stein J; Hoelzer D; Mitrou P S  
CS Department of Internal Medicine III, Hematology/Oncology, Johann Wolfgang Goethe-University Hospital, Frankfurt, Germany.  
SO ANNALS OF HEMATOLOGY, (2000 Sep) 79 (9) 485-92. *date!*  
Journal code: 9107334. ISSN: 0939-5555.  
CY GERMANY: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200010  
ED Entered STN: 20010322  
Last Updated on STN: 20010322  
Entered Medline: 20001031  
AB Induction of apoptosis in vitro using **gemcitabine** (dFdC) in combination with cladribine (2-CdA) and other cytotoxic drugs on malignant mononuclear cells (MNCs) of patients with acute myeloid leukemia (AML, n=20) and chronic lymphocytic leukemia (CLL, n=20) in myeloid (HL60, HEL) and lymphatic cell lines (HUT78, JURKAT) was investigated using different incubation conditions (simultaneous and consecutive). Furthermore, the influence of dFdC on the level of intracellular metabolites of 2-CdA was studied using high-performance liquid chromatography (HPLC). Apoptosis was evaluated using flow cytometry with 7-aminoactinomycin D. In MNCs of patients with CLL, dFdC + 2-CdA showed an antagonistic effect when applied simultaneously. This antagonism was reduced by consecutive application. The combination of dFdC with **doxorubicin** was **synergistic**, independent of incubation schedule. In blasts from newly diagnosed patients with de novo AML, all drug combinations (dFdC+2-CdA, **doxorubicin**, or cytosine arabinoside) were antagonistic by simultaneous incubation. Reduced antagonism or even **synergism** was shown (P<0.001) by consecutive incubation. The simultaneous combination of dFdC with 2-CdA in all tested cell lines resulted in a competitive inhibition on the rate of apoptosis. By changing the incubation period to a consecutive schedule, the antagonism was diminished or **synergism** of apoptosis was measured (P< 0.001). Using similar incubation conditions, these experiments were supported by HPLC measurement of intracellular metabolites of 2-CdA influenced by dFdC application. In conclusion, we demonstrated that the efficacy of dFdC in vitro in combination with other cytotoxic drugs depends on the incubation condition and on the origin of neoplastic cells (lymphatic vs myeloid). The data suggest that simultaneous combination therapy with purine and pyrimidine analogues may not improve the clinical efficacy of one or the

other drug administered alone.

L7 ANSWER 5 OF 18 MEDLINE  
AN 2000306610 MEDLINE  
DN 20306610 PubMed ID: 10850437  
TI Enhancement of Fas-mediated apoptosis in renal cell carcinoma cells by adriamycin.  
AU Wu X X; Mizutani Y; Kakehi Y; Yoshida O; Ogawa O  
CS Department of Urology, Faculty of Medicine, Kyoto University, Japan.  
SO CANCER RESEARCH, (2000 Jun 1) 60 (11) 2912-8.  
Journal code: 2984705R. ISSN: 0008-5472.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200006  
ED Entered STN: 20000714  
Last Updated on STN: 20000714  
Entered Medline: 20000630  
AB Anti-Fas monoclonal antibody (mAb) kills Fas-expressing cells by apoptosis. Several anticancer agents also mediate apoptosis and may share common intracellular pathways leading to apoptosis with Fas. Thus, we reasoned that combination treatment of drug-resistant cells with anti-Fas mAb and drugs might overcome their resistance. We investigated whether anticancer agents enhance Fas-mediated apoptosis and cytotoxicity against renal cell carcinoma (RCC) cells. Treatment of ACHN RCC cells with anti-Fas mAb in combination with 5-fluorouracil, vinblastine, IFN-alpha, or IFN-gamma did not overcome resistance to these agents. However, combination treatment with anti-Fas mAb and Adriamycin (ADR) resulted in a **synergistic** cytotoxic effect. Furthermore, **synergy** was also obtained even when the exposure time was shortened from 24 h to 8 or 2 h. **Synergy** was also achieved in four other RCC cell lines and five freshly derived human RCC cells. Treatment with anti-Fas mAb in combination with epirubicin or pirarubicin also resulted in a **synergistic** cytotoxic effect on ACHN cells. Similar results were achieved with a combination of humanized anti-Fas mAb and ADR. Incubation of ACHN cells with ADR augmented the expression of Fas and p53, but not Bcl-2, Bax, or caspase-3. However, the activity of caspase-3 itself was apparently enhanced after treatment with ADR alone or combined treatment with anti-Fas mAb. The **synergy** obtained in cytotoxicity with anti-Fas mAb and ADR was also achieved in apoptosis. Exposure of ACHN cells and freshly derived RCC cells to ADR enhanced their susceptibility to lysis by peripheral blood lymphocytes and tumor-infiltrating lymphocytes. This study demonstrates that combination treatment of RCC cells with anti-Fas mAb and ADR might overcome their resistance. The sensitization required a low concentration of ADR and a short exposure time, thus supporting the potential in vivo application of a combination of ADR and anti-Fas mAb or immunotherapy in the treatment of ADR- and/or immunotherapy-resistant RCC.

L7 ANSWER 6 OF 18 MEDLINE  
AN 1999257002 MEDLINE  
DN 99257002 PubMed ID: 10327070  
TI Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers.  
AU Pegram M; Hsu S; Lewis G; Pietras R; Beryt M; Sliwkowski M; Coombs D; Baly D; Kabbinavar F; Slamon D  
CS Division of Hematology-Oncology, UCLA School of Medicine, Los Angeles, California 90095, USA.  
SO ONCOGENE, (1999 Apr 1) 18 (13) 2241-51.  
Journal code: 8711562. ISSN: 0950-9232.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English

FS Priority Journals  
EM 199905  
ED Entered STN: 19990607  
Last Updated on STN: 20000303  
Entered Medline: 19990526

AB Previous studies have demonstrated a **synergistic** interaction between rhuMab HER2 and the cytotoxic drug cisplatin in human breast and ovarian cancer cells. To define the nature of the interaction between rhuMab HER2 and other classes of cytotoxic drugs, we applied multiple drug effect/combination index (CI) isobologram analysis to a variety of chemotherapeutic drug/rhuMab HER2 combinations in vitro. **Synergistic** interactions at clinically relevant drug concentrations were observed for rhuMab HER2 in combination with cisplatin (CI=0.48, P=0.003), thiotepa (CI=0.67, P=0.0008), and etoposide (CI=0.54, P=0.0003). Additive cytotoxic effects were observed with rhuMab HER2 plus **doxorubicin** (CI=1.16, P=0.13), paclitaxel (CI=0.91, P=0.21), methotrexate (CI=1.15, P=0.28), and vinblastine (CI=1.09, P=0.26). One drug, 5-**fluorouracil**, was found to be antagonistic with rhuMab HER2 in vitro (CI=2.87, P=0.0001). In vivo drug/rhuMab HER2 studies were conducted with HER-2/neu-transfected, MCF7 human breast cancer xenografts in athymic mice. Combinations of rhuMab HER2 plus cyclophosphamide, **doxorubicin**, paclitaxel, methotrexate, etoposide, and vinblastine in vivo resulted in a significant reduction in xenograft volume compared to chemotherapy alone (P<0.05). Xenografts treated with rhuMab HER2 plus 5-**fluorouracil** were not significantly different from 5-**fluorouracil** alone controls consistent with the subadditive effects observed with this combination in vitro. The **synergistic** interaction of rhuMab HER2 with alkylating agents, platinum analogs and topoisomerase II inhibitors, as well as the additive interaction with taxanes, **anthracyclines** and some antimetabolites in HER-2/neu-overexpressing breast cancer cells demonstrates that these are rational combinations to test in human clinical trials.

L7 ANSWER 7 OF 18 MEDLINE  
AN 1999066350 MEDLINE  
DN 99066350 PubMed ID: 9849488  
TI Enhancement of chemotherapeutic drug toxicity to human tumour cells in vitro by a subset of non-steroidal anti-inflammatory drugs (NSAIDs).  
AU Duffy C P; Elliott C J; O'Connor R A; Heenan M M; Coyle S; Cleary I M; Kavanagh K; Verhaegen S; O'Loughlin C M; NicAmhlaoibh R; Clynes M  
CS National Cell and Tissue Culture Centre, Dublin City University, Glasnevin, Ireland.  
SO EUROPEAN JOURNAL OF CANCER, (1998 Jul) 34 (8) 1250-9.  
Journal code: 9005373. ISSN: 0959-8049.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199812  
ED Entered STN: 19990115  
Last Updated on STN: 19990115  
Entered Medline: 19981216

AB The effect on cytotoxicity of combining a range of clinically important non-steroidal anti-inflammatory drugs (NSAIDs) with a variety of chemotherapeutic drugs was examined in the human lung cancer cell lines DLKP, A549, COR L23P and COR L23R and in a human leukaemia line HL60/ADR. A specific group of NSAIDs (indomethacin, sulindac, tolmetin, acemetacin, zomepirac and mefenamic acid) all at non-toxic levels, significantly increased the cytotoxicity of the **anthracyclines** (**doxorubicin**, **daunorubicin** and **epirubicin**), as well as teniposide, VP-16 and vincristine, but not the other vinca alkaloids vinblastine and vinorelbine. A substantial number of other anticancer drugs, including methotrexate, 5-**fluorouracil**, cytarabine, hydroxyurea, chlorambucil, cyclophosphamide, cisplatin, carboplatin,

mitoxantrone, actinomycin D, bleomycin, paclitaxel and camptothecin, were also tested, but displayed no **synergy** in combination with the NSAIDs. The **synergistic** effect was concentration dependent. The effect appears to be independent of the cyclo-oxygenase inhibitory ability of the NSAIDs, as (i) the **synergistic** combination could not be reversed by the addition of prostaglandins D2 or E2; (ii) sulindac sulphone, a metabolite of sulindac that does not inhibit the cyclooxygenase enzyme, was positive in the combination assay; and (iii) many NSAIDs known to be cyclo-oxygenase inhibitors, e.g. meclofenamic acid, diclofenac, naproxen, fenoprofen, phenylbutazone, flufenamic acid, flurbiprofen, ibuprofen and ketoprofen, were inactive in the combination assay. The enhancement of cytotoxicity was observed in a range of drug sensitive tumour cell lines, but did not occur in P-170-overexpressing multidrug resistant cell lines. However, in the HL60/ADR and COR L23R cell lines, in which multidrug resistance is due to overexpression of the multidrug resistance-associated protein MRP, a significant increase in cytotoxicity was observed in the presence of the active NSAIDs. Subsequent Western blot analysis of the drug sensitive parental cell lines, DLKP and A549, revealed that they also expressed MRP and reverse-transcription-polymerase chain reaction studies demonstrated that mRNA for MRP was present in both cell lines. It was found that the positive NSAIDs were among the more potent inhibitors of [3H]-LTC4 transport into inside-out plasma membrane vesicles prepared from MRP-expressing cells, of **doxorubicin** efflux from preloaded cells and of glutathione-S-transferase activity. The NSAIDs did not enhance cellular sensitivity to radiation. The combination of specific NSAIDs with anticancer drugs reported here may have potential clinical applications, especially in the circumvention of MRP-mediated multidrug resistance.

L7 ANSWER 8 OF 18 MEDLINE  
AN 1998321981 MEDLINE  
DN 98321981 PubMed ID: 9660544  
TI Combination of cisplatin-procaine complex DPR with anticancer drugs increases cytotoxicity against ovarian cancer cell lines.  
AU Viale M; Pastrone I; Pellicchia C; Vannozzi M O; Cafaggi S; Esposito M  
CS Istituto Nazionale per la Ricerca sul Cancro, Servizio di Farmacologia Tossicologica, Genova, Italy.  
SO ANTI-CANCER DRUGS, (1998 Jun) 9 (5) 457-63.  
Journal code: 9100823. ISSN: 0959-4973.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199809  
ED Entered STN: 19980925  
Last Updated on STN: 20000303  
Entered Medline: 19980917  
AB DPR, cis-diamminechloro-[2-(diethylamino)ethyl 4-amino-benzoate, N4]-chlorideplatinum(II) monohydrochloride monohydrate, is a newly developed water-soluble platinum compound which possess minimal cross-resistance to cisplatin and shows relatively less side effects. In an attempt to establish whether the combination of DPR with other conventional anticancer drugs would be of any benefit we assessed in vitro the cytotoxic effects of combinations of DPR with the antimetabolites 5-**fluorouracil** (5-FU) and methotrexate (MTX), the alkylating agents mitomycin C (MMC) and cisplatin, the antimicrotubule agent taxol (TAX), and the intercalating agent of the **anthracycline** group **doxorubicin** (DOX) on murine M5076 ovarian reticulosarcoma and human A2780 ovarian carcinoma cells. These agents were selected because of their common use in the clinic and because they represent four distinct categories of antineoplastic mechanisms. Cells were incubated for 72 h in the presence of single or combined drugs, and the cytotoxic effect was determined by the MTT assay. The analysis of combination treatment was made by the isobole method. In human A2780 cells, an overall

**synergy** was found for DPR combined with 5-FU, DOX and cisplatin. **Synergistic** effects were also observed for most combinations with MTX or MMC. A DPR concentration-dependent additivity and antagonism was seen at the highest MTX concentration (1 microM), while additive effects were observed for the combined treatments of DPR and low concentrations of MMC (0.008 and 0.0016 microM). Additive effects were also observed for the association of DPR and TAX over most combinations tested. In murine M5076 cells, **synergism** was the prevailing result observed when DPR was combined with 5-FU, DOX, MMC or cisplatin. When administered together with MTX we observed additivity over most combinations tested. These findings suggest that DPR, when simultaneously administered with standard anticancer agents, may be advantageous for cytokilling.

L7 ANSWER 9 OF 18 MEDLINE  
 AN 1998287317 MEDLINE  
 DN 98287317 PubMed ID: 9624253  
 TI In vitro modulation of **doxorubicin** and docetaxel antitumoral activity by methyl-beta-cyclodextrin.  
 AU Grosse P Y; Bressolle F; Pinguet F  
 CS Department of Oncological Pharmacology, Val d'Aurelle Anticancer Center, parc Euromedecine, Montpellier, France.  
 SO EUROPEAN JOURNAL OF CANCER, (1998 Jan) 34 (1) 168-74.  
 Journal code: 9005373. ISSN: 0959-8049.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199806  
 ED Entered STN: 19980625  
 Last Updated on STN: 19980625  
 Entered Medline: 19980618  
 AB Methyl-beta-cyclodextrin (MEBCD) was investigated for its effect on the antitumoral activity of various antineoplastic agents (**doxorubicin** (DOX), docetaxel (DXL), 5-**fluorouracil** (5-FU) and cisplatin (CDDP)) in three different human parental sensitive cancer cell lines (K562 S, MCF7 S and A2780 S) and their multidrug resistant variant sublines (K562 R, MCF7 R and A2780 R). At non-cytotoxic concentrations, MEBCD was able to increase significantly DOX and DXL cytotoxic activity in all the cell lines tested. The sensitisation ratios (IC50 drug control/IC50 drug-MEBCD treated) ranged from 311 to 14.3. Moreover, intracellular DOX accumulation, determined by high-performance liquid chromatography, was also increased when cells were treated with MEBCD combined with DOX (approximately 2-3 fold). The effects of MEBCD in resistant sublines were greater than in their parental sensitive cell lines. Other experiments demonstrated that the action of the MEBCD was independent of DOX. These data provided a basis for the potential therapeutic application of MEBCD in cancer therapy.

L7 ANSWER 10 OF 18 MEDLINE  
 AN 97338728 MEDLINE  
 DN 97338728 PubMed ID: 9195288  
 TI Preclinical studies of the combination of angiogenic inhibitors with cytotoxic agents.  
 AU Kakeji Y; Teicher B A  
 CS Dana-Farber Cancer Institute, Boston, MA 021150, USA.  
 SO INVESTIGATIONAL NEW DRUGS, (1997) 15 (1) 39-48.  
 Journal code: 8309330. ISSN: 0167-6997.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199708  
 ED Entered STN: 19970908  
 Last Updated on STN: 19980206

Entered Medline: 19970826

AB TNP-740, minocycline, suramin and genistein have demonstrated antiangiogenic activity in various experimental systems. The effect of these agents alone and in two agent combinations on the number of intratumoral vessels and response to cytotoxic anticancer therapies was assessed in animals bearing the Lewis lung carcinoma. Treatment with each of the antiangiogenic agents alone and in two agent combinations decreased the number of intratumoral vessels visualized by CD31 or Factor VIII staining to 30% to 50% of the number in the untreated control tumors. In general, the antiangiogenic agents are more effective adjuvants to cytotoxic therapies when used as two agent combinations than as single agents. The most effective antiangiogenic combinations were: TNP-470/minocycline > TNP-470/genistein > TNP-470/suramin. The increases in the response of the primary tumor to cyclophosphamide, adriamycin, CDDP, BCNU, x-rays or 5-**fluorouracil** and the lung metastases occur to about the same level with the addition of antiangiogenic agents to the therapies. With the treatment combination TNP-470/minocycline/cyclophosphamide 40% of the animals were cured. The results of these studies indicate that antiangiogenic agents can be very useful additions to treatment regimens for solid tumors.

L7 ANSWER 11 OF 18 MEDLINE

AN 97330659 MEDLINE

DN 97330659 PubMed ID: 9187118

TI Enhanced antitumor activity of combination radioimmunotherapy (131I-labeled monoclonal antibody A33) with chemotherapy (**fluorouracil**).

AU Tschmelitsch J; Barendswaard E; Williams C Jr; Yao T J; Cohen A M; Old L J; Welt S

CS New York Branch, Ludwig Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, New York 10021, USA.

NC CA-08748 (NCI)

SO CANCER RESEARCH, (1997 Jun 1) 57 (11) 2181-6.

Journal code: 2984705R. ISSN: 0008-5472.

CY United States

DT (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199707

ED Entered STN: 19970721

Last Updated on STN: 19970721

Entered Medline: 19970710

AB Monoclonal antibody (mAb) A33 reacts with an antigen expressed by >95% of colon cancer and normal colon epithelial cells. An earlier Phase I trial of 131I-labeled mAb A33 (131I-mAb A33) demonstrated bone marrow suppression as the dose-limiting toxicity, and although modest antitumor effects were seen, no normal colon toxicity was observed. In this study, a nude mouse model was used to test whether combinations of low-dose 131I-mAb A33 (0.1 mCi) and chemotherapy [5-**fluorouracil** (5-FU) or 5-FU + leucovorin, **doxorubicin**, or carmustine] enhance the antitumor effects, compared to 131I-mAb A33 alone or either drug regimen alone. 5-FU was administered either at 30 mg/kg/day for 5 days or at 75 mg/kg/day on days 1 and 5. In assessing the reduction in tumor volumes over the first 28 days of the experiment, 5-FU treatment (with or without leucovorin) in combination with 131I-mAb A33 showed a statistically significant additive antitumor effect compared to 131I-mAb A33 alone or to chemotherapy alone. When long-term survival was used as an end point, 38% of the mice treated with 5-FU and 131I-mAb A33 were disease free at 276 days compared to none from any other group, suggesting a **synergistic** effect. These data indicate that Phase II clinical trials combining radiolabeled antibody therapy with 5-FU-based treatments are warranted.

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l3/THU and synerg? and metastasis and tumor and antineoplastic

9 L3  
 477649 THU/RL  
 7 L3/THU  
 (L3 (L) THU/RL)  
 83039 SYNERG?  
 25253 METASTASIS  
 4 METASTASISES  
 10239 METASTASES  
 30116 METASTASIS  
 (METASTASIS OR METASTASISES OR METASTASES)  
 265654 TUMOR  
 111364 TUMORS  
 303054 TUMOR  
 (TUMOR OR TUMORS)  
 8615 ANTINEOPLASTIC  
 374 ANTINEOPLASTICS  
 8779 ANTINEOPLASTIC  
 (ANTINEOPLASTIC OR ANTINEOPLASTICS)

L9 1 L3/THU AND SYNERG? AND METASTASIS AND TUMOR AND ANTINEOPLASTIC

=> dis l9 ibib abs hitstr

L9 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:608574 CAPLUS

DOCUMENT NUMBER: 133:187946

TITLE: Antitumour **synergistic** combination of  
 daunorubicin derivative and topoisomerase II inhibitor  
 INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele;  
 Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 13 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050032	A1	20000831	WO 2000-EP745	20000131
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1165069	A1	20020102	EP 2000-903657	20000131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008453	A	20020129	BR 2000-8453	20000131
JP 2002537333	T2	20021105	JP 2000-600643	20000131
PRIORITY APPLN. INFO.: GB 1999-4387 A 19990225				
WO 2000-EP745 W 20000131				

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin (I) or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an **antineoplastic** topoisomerase II inhibitor in the treatment of **tumors** and the use of the



combination in the treatment or prevention of **metastasis** or in the treatment of **tumors** by inhibition of angiogenesis are disclosed. A dose of 13 mg/kg of doxorubicin alone (day +3) and a dose of 1.5 mg/kg I alone (days +1,2) were assocd., without toxicity, with an increase in the lifespan (ILS) values of 50 and 67%, resp. Combining doxorubicin at the same doses with the same schedule an increase in the antitumor activity with ILS values of 150% was obsd., indicating a **synergistic** effect of the combination.

IT 148429-22-5

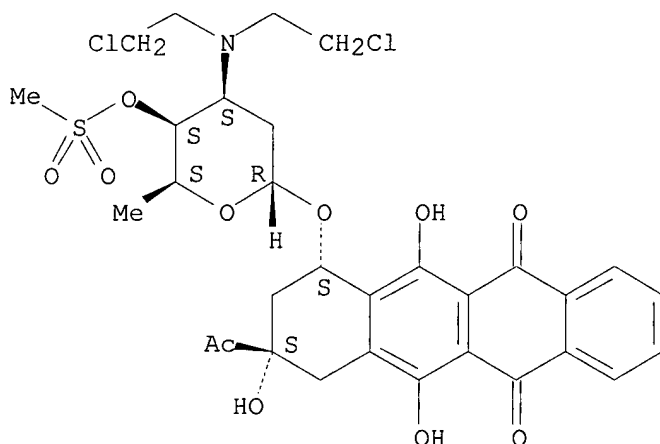
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(antitumor **synergistic** combination of daunorubicin deriv. and topoisomerase II inhibitor)

RN 148429-22-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

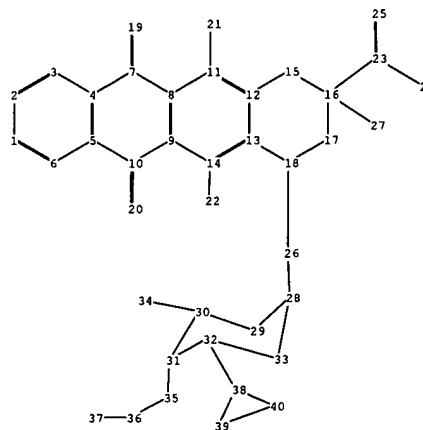
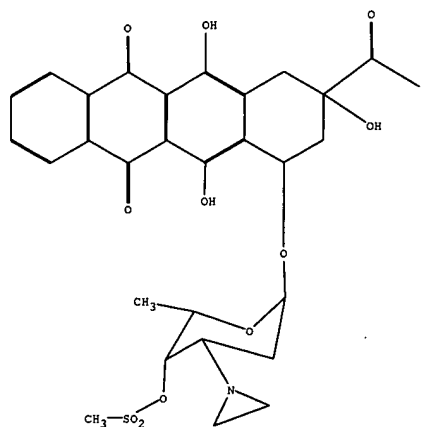
4

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

---Logging off of STN---

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chain nodes :

19 20 21 22 23 24 25 26 27 34 35 36 37

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 28 29 30 31 32 33 38  
39 40

chain bonds :

7-19 10-20 11-21 14-22 16-23 16-27 18-26 23-24 23-25 26-28 30-34 31-35 32-38  
35-36 36-37

ring bonds :

1-2 1-6 2-3 3-4 4-5 4-7 5-6 5-10 7-8 8-9 8-11 9-10 9-14 11-12 12-13 12-15  
13-14 13-18 15-16 16-17 17-18 28-29 28-33 29-30 30-31 31-32 32-33 38-39 38-40  
39-40

exact/norm bonds :

4-7 5-10 7-8 7-19 9-10 10-20 11-21 12-15 13-18 14-22 15-16 16-17 16-27 17-18  
18-26 23-25 26-28 28-29 28-33 29-30 30-31 31-32 31-35 32-33 32-38 35-36 38-39  
38-40 39-40

exact bonds :

16-23 23-24 30-34 36-37

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-11 9-14 11-12 12-13 13-14

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom  
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS 20:CLASS  
21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:Atom 29:Atom  
30:Atom 31:Atom 32:Atom 33:Atom 34:CLASS 35:CLASS 36:CLASS 37:CLASS 38:CLASS  
39:CLASS 40:CLASS

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PASSWORD:

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NEWS	3	Apr 09 BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS	4	Apr 09 ZDB will be removed from STN
NEWS	5	Apr 19 US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS	6	Apr 22 Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS	7	Apr 22 BIOSIS Gene Names now available in TOXCENTER
NEWS	8	Apr 22 Federal Research in Progress (FEDRIP) now available
NEWS	9	Jun 03 New e-mail delivery for search results now available
NEWS	10	Jun 10 MEDLINE Reload
NEWS	11	Jun 10 PCTFULL has been reloaded
NEWS	12	Jul 02 FOREGE no longer contains STANDARDS file segment
NEWS	13	Jul 22 USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS	14	Jul 29 Enhanced polymer searching in REGISTRY
NEWS	15	Jul 30 NETFIRST to be removed from STN
NEWS	16	Aug 08 CANCERLIT reload
NEWS	17	Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN
NEWS	18	Aug 08 NTIS has been reloaded and enhanced
NEWS	19	Aug 19 Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS	20	Aug 19 IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS	21	Aug 19 The MEDLINE file segment of TOXCENTER has been reloaded
NEWS	22	Aug 26 Sequence searching in REGISTRY enhanced
NEWS	23	Sep 03 JAPIO has been reloaded and enhanced
NEWS	24	Sep 16 Experimental properties added to the REGISTRY file
NEWS	25	Sep 16 Indexing added to some pre-1967 records in CA/CAPLUS
NEWS	26	Sep 16 CA Section Thesaurus available in CAPLUS and CA
NEWS	27	Oct 01 CASREACT Enriched with Reactions from 1907 to 1985
NEWS	28	Oct 21 EVENTLINE has been reloaded
NEWS	29	Oct 24 BEILSTEIN adds new search fields
NEWS	30	Oct 24 Nutraceuticals International (NUTRACEUT) now available on STN
NEWS	31	Oct 25 MEDLINE SDI run of October 8, 2002
NEWS	32	Nov 18 DKILIT has been renamed APOLLIT
NEWS	33	Nov 25 More calculated properties added to REGISTRY
NEWS EXPRESS		October 14 CURRENT WINDOWS VERSION IS V6.01, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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NEWS INTER		General Internet Information
NEWS LOGIN		Welcome Banner and News Items
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FILE 'HOME' ENTERED AT 10:20:31 ON 28 NOV 2002

=> index medicine

FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED  
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT, CAPLUS,  
CEN, DDFB, DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU,  
EMBAL, EMBASE, ESBIODBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI,  
MEDICONF, MEDLINE, NAPRALERT, NLDB, ...' ENTERED AT 10:21:08 ON 28 NOV 2002

36 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view  
search error messages that display as 0\* with SET DETAIL OFF.

=> s anthracycline

1347	FILE ADISALERTS
106	FILE ADISINSIGHT
172	FILE ADISNEWS
6133	FILE BIOSIS
1606	FILE BIOTECHNO
8188	FILE CANCERLIT
5576	FILE CAPLUS
3	FILE CEN
330	FILE DDFB
3870	FILE DDFU
234	FILE DGENE
330	FILE DRUGB
6	FILE DRUGLAUNCH
102	FILE DRUGNL
4883	FILE DRUGU
52	FILE EMBAL
7786	FILE EMBASE
3401	FILE ESBIODBASE
427	FILE IFIPAT
206	FILE IPA
1652	FILE JICST-EPLUS
1	FILE KOSMET
922	FILE LIFESCI
1	FILE MEDICONF
7535	FILE MEDLINE
140	FILE NAPRALERT
382	FILE NLDB
9262	FILE PASCAL
64	FILE PHARMAML
248	FILE PHIN
5428	FILE SCISEARCH
10426	FILE TOXCENTER
1863	FILE USPATFULL
23	FILE USPAT2

34 FILES HAVE ONE OR MORE ANSWERS, 36 FILES SEARCHED IN STNINDEX

L1 QUE ANTHRACYCLINE

=> s l1 and (daunorubicin or doxorubicin)

471 FILE ADISALERTS  
81 FILE ADISINSIGHT  
65 FILE ADISNEWS  
1748 FILE BIOSIS  
824 FILE BIOTECHNO  
3761 FILE CANCERLIT  
1749 FILE CAPLUS  
186 FILE DDFB  
1843 FILE DDFU  
30 FILE DGENE  
186 FILE DRUGB  
25 FILE DRUGNL  
2369 FILE DRUGU  
19 FILE EMBAL  
4305 FILE EMBASE  
1291 FILE ESBIODBASE  
161 FILE IFIPAT  
80 FILE IPA  
157 FILE JICST-EPLUS  
1 FILE KOSMET

23 FILES SEARCHED...

323 FILE LIFESCI  
3707 FILE MEDLINE  
8 FILE NAPRALERT  
121 FILE NLDB  
4161 FILE PASCAL  
19 FILE PHARMAML  
80 FILE PHIN  
1836 FILE SCISEARCH  
4375 FILE TOXCENTER  
1341 FILE USPATFULL  
18 FILE USPAT2

31 FILES HAVE ONE OR MORE ANSWERS, 36 FILES SEARCHED IN STNINDEX

L2 QUE L1 AND (DAUNORUBICIN OR DOXORUBICIN)

=> s l1 and (daunorubicin or doxorubicin)

526 FILE ADISALERTS  
85 FILE ADISINSIGHT  
68 FILE ADISNEWS  
2315 FILE BIOSIS  
1045 FILE BIOTECHNO  
4655 FILE CANCERLIT  
2222 FILE CAPLUS  
223 FILE DDFB  
2177 FILE DDFU  
38 FILE DGENE  
223 FILE DRUGB  
27 FILE DRUGNL  
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143 FILE NLDB  
4743 FILE PASCAL

20 FILE PHARMAML  
84 FILE PHIN  
2164 FILE SCISEARCH  
5319 FILE TOXCENTER  
1418 FILE USPATFULL  
18 FILE USPAT2

31 FILES HAVE ONE OR MORE ANSWERS, 36 FILES SEARCHED IN STNINDEX

L3 QUE L1 AND (DAUNORUBICIN OR DOXORUBICIN)

=> s l3 and synerg?

20 FILE ADISALERTS  
8 FILE ADISINSIGHT  
2 FILE ADISNEWS  
46 FILE BIOSIS  
20 FILE BIOTECHNO  
194 FILE CANCERLIT  
53 FILE CAPLUS  
96 FILE DDFU  
144 FILE DRUGU

16 FILES SEARCHED...

1 FILE EMBAL  
70 FILE EMBASE  
47 FILE ESBIODBASE  
6 FILE IFIPAT  
4 FILE JICST-EPLUS  
4 FILE LIFESCI  
184 FILE MEDLINE  
9 FILE NLDB  
131 FILE PASCAL  
2 FILE PHARMAML  
6 FILE PHIN  
44 FILE SCISEARCH  
206 FILE TOXCENTER  
305 FILE USPATFULL  
6 FILE USPAT2

24 FILES HAVE ONE OR MORE ANSWERS, 36 FILES SEARCHED IN STNINDEX

L4 QUE L3 AND SYNERG?

=> s l4 and (metastasis or tumor or cancer or neoplastic)

16 FILE ADISALERTS  
8 FILE ADISINSIGHT  
2 FILE ADISNEWS  
34 FILE BIOSIS  
15 FILE BIOTECHNO  
156 FILE CANCERLIT

6 FILES SEARCHED...

38 FILE CAPLUS  
79 FILE DDFU  
123 FILE DRUGU

17 FILES SEARCHED...

58 FILE EMBASE  
45 FILE ESBIODBASE  
6 FILE IFIPAT  
4 FILE JICST-EPLUS  
3 FILE LIFESCI  
144 FILE MEDLINE  
9 FILE NLDB  
109 FILE PASCAL

29 FILES SEARCHED...

2 FILE PHARMAML

6 FILE PHIN  
33 FILE SCISEARCH  
153 FILE TOXCENTER  
302 FILE USPATFULL  
6 FILE USPAT2

23 FILES HAVE ONE OR MORE ANSWERS, 36 FILES SEARCHED IN STNINDEX

L5 QUE L4 AND (METASTASIS OR TUMOR OR CANCER OR NEOPLASTIC)

=> file cancerlit

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

5.30

5.51

FILE 'CANCERLIT' ENTERED AT 10:26:52 ON 28 NOV 2002

FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l4 and (gemcitabine or fluoropyrimidine or fluorouracil or cytidine)

6839 ANTHRACYCLINE

2868 ANTHRACYCLINES

8188 ANTHRACYCLINE

(ANTHRACYCLINE OR ANTHRACYCLINES)

5723 DAUNORUBICIN

4 DAUNORUBICINS

5723 DAUNORUBICIN

(DAUNORUBICIN OR DAUNORUBICINS)

25341 DOXORUBICIN

3 DOXORUBICINS

25341 DOXORUBICIN

(DOXORUBICIN OR DOXORUBICINS)

23655 SYNERG?

2038 GEMCITABINE

496 FLUOROPYRIMIDINE

465 FLUOROPYRIMIDINES

815 FLUOROPYRIMIDINE

(FLUOROPYRIMIDINE OR FLUOROPYRIMIDINES)

25652 FLUOROURACIL

16 FLUOROURACILS

25653 FLUOROURACIL

(FLUOROURACIL OR FLUOROURACILS)

1721 CYTIDINE

22 CYTIDINES

1735 CYTIDINE

(CYTIDINE OR CYTIDINES)

L6 22 L4 AND (GEMCITABINE OR FLUOROPYRIMIDINE OR FLUOROURACIL OR CYTIDINE)

=> dis l6 1-22 bib abs

L6 ANSWER 1 OF 22 CANCERLIT

AN 2002176015 CANCERLIT

DN 22160464 PubMed ID: 12170449

TI Docetaxel in the treatment of breast cancer: an update on recent studies.

AU Nabholz Jean-Marc A; Reese David M; Lindsay Mary-Ann; Riva Alessandro

CS Cancer Therapy Development Program, Jonsson Comprehensive Cancer Center,  
University of California, Los Angeles, CA 90095-7077, USA.

SO SEMINARS IN ONCOLOGY, (2002 Jun) 29 (3 Suppl 12) 28-34. Ref: 23  
Journal code: 0420432. ISSN: 0093-7754.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LA English

FS MEDLINE; Priority Journals

OS MEDLINE 2002415865

EM 200208

ED Entered STN: 20021018  
Last Updated on STN: 20021018

AB Recently there has been great interest in developing combination regimens  
involving taxanes and **anthracyclines** for the treatment of  
advanced breast cancer. Docetaxel in particular has substantial activity  
when combined with **doxorubicin**. In one randomized trial, the  
combination of **doxorubicin** 50 mg/m<sup>2</sup> and docetaxel 75 mg/m<sup>2</sup>  
showed significantly greater activity than **doxorubicin** plus  
cyclophosphamide (AC), producing a higher response rate (60% v 47%) and  
longer time to progression. In a second study, 484 patients were  
randomized to receive either docetaxel plus **doxorubicin** and  
cyclophosphamide (TAC) or 5-fluorouracil plus **doxorubicin** and  
cyclophosphamide. The response rate was significantly higher in the TAC  
arm (54% v 42%), including patients with unfavorable prognostic factors.  
Febrile neutropenia occurred more frequently in patients receiving TAC,  
but the incidence of infection and septic death was low and no greater  
than in the 5-fluorouracil/**doxorubicin**/cyclophosphamide arm. TAC  
was not associated with an increased risk of cardiotoxicity. Data on time  
to progression and survival are not yet available. The TAC and  
**doxorubicin**/docetaxel regimens have been compared with  
non-docetaxel-containing programs in randomized adjuvant trials which have  
completed accrual but are not yet mature. A second generation of adjuvant  
trials compares sequential versus synchronous docetaxel-based  
polychemotherapy. In addition, based on preclinical data suggesting a  
**synergistic** interaction between docetaxel, platinum salts, and  
trastuzumab, as well as preliminary data from pilot studies in patients  
with HER2-positive metastatic disease showing tolerability and activity,  
adjuvant studies of this novel three-agent combination are in progress in  
patients with HER2-positive early breast cancer.  
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L6 ANSWER 2 OF 22      CANCERLIT

AN 2002161380      CANCERLIT

DN 21830591      PubMed ID: 11841932

TI Future treatment options-with capecitabine in solid tumours.

AU Wilke H

CS Department of Internal Medicine and Oncology/Hematology, Kliniken  
Essen-Mitte, Germany.. hwilke@kem.telba.de

SO EUROPEAN JOURNAL OF CANCER, (2002 Feb) 38 Suppl 2 21-5.  
Journal code: 9005373. ISSN: 0959-8049.

CY England: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS MEDLINE; Priority Journals

OS MEDLINE 2002109922

EM 200207

ED Entered STN: 20020819  
Last Updated on STN: 20020819

AB The oral **fluoropyrimidine**, capecitabine is attracting great  
interest in the context of tumour-selective therapy and rationally  
designed combination regimens. Agents such as taxanes upregulate thymidine  
phosphorylase (TP), and there is therefore a clear rationale for their



combination with capecitabine. Preclinical studies of capecitabine/taxane combination therapy demonstrated **synergistic** antitumour activity and phase I studies showed encouraging efficacy. Therefore, a randomised, phase III trial (docetaxel versus docetaxel/capecitabine) has been initiated in **anthracycline**-refractory metastatic breast cancer patients. Recruitment is complete. In colorectal cancer, capecitabine/oxaliplatin combination therapy is promising and a phase I, dose-finding trial has been conducted in patients with refractory metastatic solid tumours. A similar trial has evaluated capecitabine/irinotecan combination treatment. Capecitabine is also being investigated as adjuvant therapy for colorectal and breast cancers. The primary objective of the ongoing X-ACT trial in almost 2000 Dukes' C colon cancer patients is to demonstrate at least equivalent disease-free survival between capecitabine and the Mayo Clinic regimen. In addition, the CALGB is planning a randomised, phase III trial of capecitabine versus **doxorubicin**/cyclophosphamide or cyclophosphamide/methotrexate/5-**fluorouracil** (CMF) as adjuvant treatment in high-risk, node-negative breast cancer patients aged >65 years.

L6 ANSWER 3 OF 22           CANCERLIT  
AN 2002095363           CANCERLIT  
DN 21551584    PubMed ID: 11694788  
TI New combinations with Herceptin in metastatic breast cancer.  
AU Winer E P; Burstein H J  
CS Dana-Farber Cancer Institute, Boston, Mass 02115, USA..  
ewiner@partners.org  
SO ONCOLOGY, (2001) 61 Suppl 2 50-7. Ref: 41  
Journal code: 0135054. ISSN: 0030-2414.  
CY Switzerland  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LA English  
FS MEDLINE; Priority Journals  
OS MEDLINE 2001641940  
EM 200112  
ED Entered STN: 20020726  
Last Updated on STN: 20020726  
AB Preclinical data indicate that trastuzumab (Herceptin) has the potential for **synergistic** or additive effects in combination with therapies including chemotherapy and hormonal agents, providing the rationale for a number of clinical trials in women with HER2-positive metastatic breast cancer. A recently reported phase II trial has demonstrated that trastuzumab plus vinorelbine is both effective (overall response rate 75%) and well tolerated, with the major side effects being typical of single-agent vinorelbine. Other combinations of trastuzumab with a variety of other chemotherapeutic and hormonal agents are also being assessed. In an effort to overcome the cardiotoxicity observed with trastuzumab plus **doxorubicin** in the pivotal phase III trial, combination regimens involving potentially less toxic **anthracyclines** such as epirubicin and liposomal formulations of **doxorubicin** are ongoing. In addition, trials are investigating whether trastuzumab can reverse the resistance to hormonal therapy that develops in most women with metastatic breast cancer. These and other studies will identify the regimens that produce the best outcomes with the fewest possible side effects in women with HER2-positive breast cancer.  
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L6 ANSWER 4 OF 22           CANCERLIT  
AN 2000496124           CANCERLIT  
DN 20496124    PubMed ID: 11043419  
TI Induction of apoptosis using 2',2' difluorodeoxycytidine (**gemcitabine**) in combination with antimetabolites or **anthracyclines** on malignant lymphatic and myeloid cells.

Antagonism or **synergism** depends on incubation schedule and origin of neoplastic cells.

AU Chow K U; Ries J; Weidmann E; Pourebrahim F; Napieralski S; Stieler M;  
Boehrer S; Rummel M J; Stein J; Hoelzer D; Mitrou P S  
CS Department of Internal Medicine III, Hematology/Oncology, Johann Wolfgang  
Goethe-University Hospital, Frankfurt, Germany.  
SO ANNALS OF HEMATOLOGY, (2000 Sep) 79 (9) 485-92.  
Journal code: 9107334. ISSN: 0939-5555.  
CY GERMANY: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS MEDLINE; Priority Journals  
OS MEDLINE 2000499428  
EM 200010  
ED Entered STN: 20010423  
Last Updated on STN: 20010423  
AB Induction of apoptosis in vitro using **gemcitabine** (dFdC) in  
combination with cladribine (2-CdA) and other cytotoxic drugs on malignant  
mononuclear cells (MNCs) of patients with acute myeloid leukemia (AML,  
n=20) and chronic lymphocytic leukemia (CLL, n =20) in myeloid (HL60, HEL)  
and lymphatic cell lines (HUT78, JURKAT) was investigated using different  
incubation conditions (simultaneous and consecutive). Furthermore, the  
influence of dFdC on the level of intracellular metabolites of 2-CdA was  
studied using high-performance liquid chromatography (HPLC). Apoptosis was  
evaluated using flow cytometry with 7-aminoactinomycin D. In MNCs of  
patients with CLL, dFdC + 2-CdA showed an antagonistic effect when applied  
simultaneously. This antagonism was reduced by consecutive application.  
The combination of dFdC with **doxorubicin** was **synergistic**  
, independent of incubation schedule. In blasts from newly diagnosed  
patients with de novo AML, all drug combinations (dFdC+2-CdA,  
**doxorubicin**, or cytosine arabinoside) were antagonistic by  
simultaneous incubation. Reduced antagonism or even **synergism**  
was shown (P<0.001) by consecutive incubation. The simultaneous  
combination of dFdC with 2-CdA in all tested cell lines resulted in a  
competitive inhibition on the rate of apoptosis. By changing the  
incubation period to a consecutive schedule, the antagonism was diminished  
or **synergism** of apoptosis was measured (P< 0.001). Using similar  
incubation conditions, these experiments were supported by HPLC  
measurement of intracellular metabolites of 2-CdA influenced by dFdC  
application. In conclusion, we demonstrated that the efficacy of dFdC in  
vitro in combination with other cytotoxic drugs depends on the incubation  
condition and on the origin of neoplastic cells (lymphatic vs myeloid).  
The data suggest that simultaneous combination therapy with purine and  
pyrimidine analogues may not improve the clinical efficacy of one or the  
other drug administered alone.

L6 ANSWER 5 OF 22 CANCERLIT  
AN 2000306610 CANCERLIT  
DN 20306610 PubMed ID: 10850437  
TI Enhancement of Fas-mediated apoptosis in renal cell carcinoma cells by  
adriamycin.  
AU Wu X X; Mizutani Y; Kakehi Y; Yoshida O; Ogawa O  
CS Department of Urology, Faculty of Medicine, Kyoto University, Japan.  
SO CANCER RESEARCH, (2000 Jun 1) 60 (11) 2912-8.  
Journal code: 2984705R. ISSN: 0008-5472.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS MEDLINE; Priority Journals  
OS MEDLINE 2000306610  
EM 200006  
ED Entered STN: 20000811  
Last Updated on STN: 20000811  
AB Anti-Fas monoclonal antibody (mAb) kills Fas-expressing cells by

apoptosis. Several anticancer agents also mediate apoptosis and may share common intracellular pathways leading to apoptosis with Fas. Thus, we reasoned that combination treatment of drug-resistant cells with anti-Fas mAb and drugs might overcome their resistance. We investigated whether anticancer agents enhance Fas-mediated apoptosis and cytotoxicity against renal cell carcinoma (RCC) cells. Treatment of ACHN RCC cells with anti-Fas mAb in combination with 5-fluorouracil, vinblastine, IFN-alpha, or IFN-gamma did not overcome resistance to these agents. However, combination treatment with anti-Fas mAb and Adriamycin (ADR) resulted in a **synergistic** cytotoxic effect. Furthermore, **synergy** was also obtained even when the exposure time was shortened from 24 h to 8 or 2 h. **Synergy** was also achieved in four other RCC cell lines and five freshly derived human RCC cells. Treatment with anti-Fas mAb in combination with epirubicin or pirarubicin also resulted in a **synergistic** cytotoxic effect on ACHN cells. Similar results were achieved with a combination of humanized anti-Fas mAb and ADR. Incubation of ACHN cells with ADR augmented the expression of Fas and p53, but not Bcl-2, Bax, or caspase-3. However, the activity of caspase-3 itself was apparently enhanced after treatment with ADR alone or combined treatment with anti-Fas mAb. The **synergy** obtained in cytotoxicity with anti-Fas mAb and ADR was also achieved in apoptosis. Exposure of ACHN cells and freshly derived RCC cells to ADR enhanced their susceptibility to lysis by peripheral blood lymphocytes and tumor-infiltrating lymphocytes. This study demonstrates that combination treatment of RCC cells with anti-Fas mAb and ADR might overcome their resistance. The sensitization required a low concentration of ADR and a short exposure time, thus supporting the potential in vivo application of a combination of ADR and anti-Fas mAb or immunotherapy in the treatment of ADR- and/or immunotherapy-resistant RCC.

L6 ANSWER 6 OF 22 CANCERLIT  
 AN 199257002 CANCERLIT  
 DN 99257002 PubMed ID: 10327070  
 TI Inhibitory effects of combinations of HER-2/neu antibody and  
 chemotherapeutic agents used for treatment of human breast cancers.  
 AU Pegram M; Hsu S; Lewis G; Pietras R; Beryt M; Sliwkowski M; Coombs D; Baly  
 D; Kabbinavar F; Slamon D  
 CS Division of Hematology-Oncology, UCLA School of Medicine, Los Angeles,  
 California 90095, USA.  
 SO ONCOGENE, (1999 Apr 1) 18 (13) 2241-51.  
 Journal code: 8711562. ISSN: 0950-9232.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS MEDLINE; Priority Journals  
 OS MEDLINE 199257002  
 EM 199905  
 ED Entered STN: 19990622  
 Last Updated on STN: 19990622  
 AB Previous studies have demonstrated a **synergistic** interaction  
 between rhuMab HER2 and the cytotoxic drug cisplatin in human breast and  
 ovarian cancer cells. To define the nature of the interaction between  
 rhuMab HER2 and other classes of cytotoxic drugs, we applied multiple drug  
 effect/combination index (CI) isobologram analysis to a variety of  
 chemotherapeutic drug/rhuMab HER2 combinations in vitro.  
**Synergistic** interactions at clinically relevant drug  
 concentrations were observed for rhuMab HER2 in combination with cisplatin  
 (CI=0.48, P=0.003), thiotepa (CI=0.67, P=0.0008), and etoposide (CI=0.54,  
 P=0.0003). Additive cytotoxic effects were observed with rhuMab HER2 plus  
**doxorubicin** (CI=1.16, P=0.13), paclitaxel (CI=0.91, P=0.21),  
 methotrexate (CI=1.15, P=0.28), and vinblastine (CI=1.09, P=0.26). One  
 drug, 5-fluorouracil, was found to be antagonistic with rhuMab  
 HER2 in vitro (CI=2.87, P=0.0001). In vivo drug/rhuMab HER2 studies were  
 conducted with HER-2/neu-transfected, MCF7 human breast cancer xenografts

in athymic mice. Combinations of rhuMAb HER2 plus cyclophosphamide, **doxorubicin**, paclitaxel, methotrexate, etoposide, and vinblastine in vivo resulted in a significant reduction in xenograft volume compared to chemotherapy alone ( $P < 0.05$ ). Xenografts treated with rhuMAb HER2 plus 5-**fluorouracil** were not significantly different from 5-**fluorouracil** alone controls consistent with the subadditive effects observed with this combination in vitro. The **synergistic** interaction of rhuMAb HER2 with alkylating agents, platinum analogs and topoisomerase II inhibitors, as well as the additive interaction with taxanes, **anthracyclines** and some antimetabolites in HER-2/neu-overexpressing breast cancer cells demonstrates that these are rational combinations to test in human clinical trials.

L6 ANSWER 7 OF 22 CANCERLIT  
 AN 1999066350 CANCERLIT  
 DN 99066350 PubMed ID: 9849488  
 TI Enhancement of chemotherapeutic drug toxicity to human tumour cells in vitro by a subset of non-steroidal anti-inflammatory drugs (NSAIDs).  
 AU Duffy C P; Elliott C J; O'Connor R A; Heenan M M; Coyle S; Cleary I M; Kavanagh K; Verhaegen S; O'Loughlin C M; NicAmhlaoibh R; Clynes M  
 CS National Cell and Tissue Culture Centre, Dublin City University, Glasnevin, Ireland.  
 SO EUROPEAN JOURNAL OF CANCER, (1998 Jul) 34 (8) 1250-9.  
 Journal code: 9005373. ISSN: 0959-8049.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS MEDLINE; Priority Journals  
 OS MEDLINE 1999066350  
 EM 199812  
 ED Entered STN: 19990127  
 Last Updated on STN: 19990127  
 AB The effect on cytotoxicity of combining a range of clinically important non-steroidal anti-inflammatory drugs (NSAIDs) with a variety of chemotherapeutic drugs was examined in the human lung cancer cell lines DLKP, A549, COR L23P and COR L23R and in a human leukaemia line HL60/ADR. A specific group of NSAIDs (indomethacin, sulindac, tolmetin, acemetacin, zomepirac and mefenamic acid) all at non-toxic levels, significantly increased the cytotoxicity of the **anthracyclines** (**doxorubicin**, **daunorubicin** and **epirubicin**), as well as teniposide, VP-16 and vincristine, but not the other vinca alkaloids vinblastine and vinorelbine. A substantial number of other anticancer drugs, including methotrexate, 5-**fluorouracil**, cytarabine, hydroxyurea, chlorambucil, cyclophosphamide, cisplatin, carboplatin, mitoxantrone, actinomycin D, bleomycin, paclitaxel and camptothecin, were also tested, but displayed no **synergy** in combination with the NSAIDs. The **synergistic** effect was concentration dependent. The effect appears to be independent of the cyclo-oxygenase inhibitory ability of the NSAIDs, as (i) the **synergistic** combination could not be reversed by the addition of prostaglandins D2 or E2; (ii) sulindac sulphone, a metabolite of sulindac that does not inhibit the cyclooxygenase enzyme, was positive in the combination assay; and (iii) many NSAIDs known to be cyclo-oxygenase inhibitors, e.g. meclofenamic acid, diclofenac, naproxen, fenoprofen, phenylbutazone, flufenamic acid, flurbiprofen, ibuprofen and ketoprofen, were inactive in the combination assay. The enhancement of cytotoxicity was observed in a range of drug sensitive tumour cell lines, but did not occur in P-170-overexpressing multidrug resistant cell lines. However, in the HL60/ADR and COR L23R cell lines, in which multidrug resistance is due to overexpression of the multidrug resistance-associated protein MRP, a significant increase in cytotoxicity was observed in the presence of the active NSAIDs. Subsequent Western blot analysis of the drug sensitive parental cell lines, DLKP and A549, revealed that they also expressed MRP and reverse-transcription-polymerase chain reaction studies demonstrated that mRNA for MRP was

present in both cell lines. It was found that the positive NSAIDs were among the more potent inhibitors of [3H]-LTC<sub>4</sub> transport into inside-out plasma membrane vesicles prepared from MRP-expressing cells, of **doxorubicin** efflux from preloaded cells and of glutathione-S-transferase activity. The NSAIDs did not enhance cellular sensitivity to radiation. The combination of specific NSAIDs with anticancer drugs reported here may have potential clinical applications, especially in the circumvention of MRP-mediated multidrug resistance.

L6 ANSWER 8 OF 22 CANCERLIT  
 AN 1998321981 CANCERLIT  
 DN 98321981 PubMed ID: 9660544  
 TI Combination of cisplatin-procaine complex DPR with anticancer drugs increases cytotoxicity against ovarian cancer cell lines.  
 AU Viale M; Pastrone I; Pellecchia C; Vannozzi M O; Cafaggi S; Esposito M  
 CS Istituto Nazionale per la Ricerca sul Cancro, Servizio di Farmacologia Tossicologica, Genova, Italy.  
 SO ANTI-CANCER DRUGS, (1998 Jun) 9 (5) 457-63.  
 Journal code: 9100823. ISSN: 0959-4973.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS MEDLINE; Priority Journals  
 OS MEDLINE 1998321981  
 EM 199809  
 ED Entered STN: 19981007  
 Last Updated on STN: 19981007  
 AB DPR, cis-diamminechloro-[2-(diethylamino)ethyl 4-amino-benzoate, N4]-chlorideplatinum(II) monohydrochloride monohydrate, is a newly developed water-soluble platinum compound which possess minimal cross-resistance to cisplatin and shows relatively less side effects. In an attempt to establish whether the combination of DPR with other conventional anticancer drugs would be of any benefit we assessed in vitro the cytotoxic effects of combinations of DPR with the antimetabolites 5-**fluorouracil** (5-FU) and methotrexate (MTX), the alkylating agents mitomycin C (MMC) and cisplatin, the antimicrotubule agent taxol (TAX), and the intercalating agent of the **anthracycline** group **doxorubicin** (DOX) on murine M5076 ovarian reticulosarcoma and human A2780 ovarian carcinoma cells. These agents were selected because of their common use in the clinic and because they represent four distinct categories of antineoplastic mechanisms. Cells were incubated for 72 h in the presence of single or combined drugs, and the cytotoxic effect was determined by the MTT assay. The analysis of combination treatment was made by the isobole method. In human A2780 cells, an overall **synergy** was found for DPR combined with 5-FU, DOX and cisplatin. **Synergistic** effects were also observed for most combinations with MTX or MMC. A DPR concentration-dependent additivity and antagonism was seen at the highest MTX concentration (1 microM), while additive effects were observed for the combined treatments of DPR and low concentrations of MMC (0.008 and 0.0016 microM). Additive effects were also observed for the association of DPR and TAX over most combinations tested. In murine M5076 cells, **synergism** was the prevailing result observed when DPR was combined with 5-FU, DOX, MMC or cisplatin. When administered together with MTX we observed additivity over most combinations tested. These findings suggest that DPR, when simultaneously administered with standard anticancer agents, may be advantageous for cytotoxicity.

L6 ANSWER 9 OF 22 CANCERLIT  
 AN 1998287317 CANCERLIT  
 DN 98287317 PubMed ID: 9624253  
 TI In vitro modulation of **doxorubicin** and docetaxel antitumoral activity by methyl-beta-cyclodextrin.  
 AU Grosse P Y; Bressolle F; Pinguet F  
 CS Department of Oncological Pharmacology, Val d'Aurelle Anticancer Center,

SO parc Euromedecine, Montpellier, France.  
EUROPEAN JOURNAL OF CANCER, (1998 Jan) 34 (1) 168-74.  
Journal code: 9005373. ISSN: 0959-8049.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS MEDLINE; Priority Journals  
OS MEDLINE 1998287317  
EM 199806  
ED Entered STN: 19980713  
Last Updated on STN: 19980713  
AB Methyl-beta-cyclodextrin (MEBCD) was investigated for its effect on the antitumoral activity of various antineoplastic agents (**doxorubicin** (DOX), docetaxel (DXL), 5-**fluorouracil** (5-FU) and cisplatin (CDDP)) in three different human parental sensitive cancer cell lines (K562 S, MCF7 S and A2780 S) and their multidrug resistant variant sublines (K562 R, MCF7 R and A2780 R). At non-cytotoxic concentrations, MEBCD was able to increase significantly DOX and DXL cytotoxic activity in all the cell lines tested. The sensitisation ratios (IC50 drug control/IC50 drug-MEBCD treated) ranged from 311 to 14.3. Moreover, intracellular DOX accumulation, determined by high-performance liquid chromatography, was also increased when cells were treated with MEBCD combined with DOX (approximately 2-3 fold). The effects of MEBCD in resistant sublines were greater than in their parental sensitive cell lines. Other experiments demonstrated that the action of the MEBCD was independent of DOX. These data provided a basis for the potential therapeutic application of MEBCD in cancer therapy.

L6 ANSWER 10 OF 22 CANCERLIT  
AN 97611890 CANCERLIT  
DN 97611890  
TI Taxoteres in combination: a step forward (Meeting abstract).  
AU Burris H 3rd  
CS Brooke Army Medical Center, Ft. Sam Houston, TX.  
SO Can J Infectious Dis, (1995) 6 (Suppl C) 224C.  
DT (MEETING ABSTRACTS)  
LA English  
FS Institute for Cell and Developmental Biology  
EM 199706  
ED Entered STN: 19980417  
Last Updated on STN: 19980417  
AB Taxotere is a hemisynthetic derivative from the European yew, which inhibits tubulin depolymerization resulting in microtubule bundle aggregates and cell death. Activity against **anthracycline** refractory breast, platinum-resistant ovarian and NSCLC, and a variety of other tumor types has been report. Combination regimens are the next logical step for increasing effectiveness in reducing tumors and prolonging survival. Bissery et al demonstrated **synergism** with Taxotere and cyclophosphamide, VP-16, and 5-FU against a variety of murine tumor, as 60% of each MTD could be administered without additional toxicity. Similar studies indicated overlap in DLT for Taxotere with CDDP or **doxorubicin**, whereas 80% of the MTD of Taxotere and VCR could be administered without additional toxicity. The MTD for Taxotere/CDDP was 100 mg/m2 q21 days with predominantly neutropenia, no increased neurotoxicity, and antitumor activity in breast, colon, head and neck, gastric, and NSCLC. Taxotere/5-FU continues with Taxotere 60 mg/m2 day 1 and 5-FU 200 mg/m2 days 1-5 having been delivered with grade IV neutropenia and no increase in gastrointestinal toxicity. Plans include evaluating Taxotere/CDDP in NSCLC, and Taxotere/5-FU in breast and gastrointestinal malignancies.

L6 ANSWER 11 OF 22 CANCERLIT  
AN 97338728 CANCERLIT  
DN 97338728 PubMed ID: 9195288

TI Preclinical studies of the combination of angiogenic inhibitors with cytotoxic agents.  
 AU Kakeji Y; Teicher B A  
 CS Dana-Farber Cancer Institute, Boston, MA 021150, USA.  
 SO INVESTIGATIONAL NEW DRUGS, (1997) 15 (1) 39-48.  
 Journal code: 8309330. ISSN: 0167-6997.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS MEDLINE; Priority Journals  
 OS MEDLINE 97338728  
 EM 199708  
 ED Entered STN: 19970909  
 Last Updated on STN: 19970909  
 AB TNP-740, minocycline, suramin and genistein have demonstrated antiangiogenic activity in various experimental systems. The effect of these agents alone and in two agent combinations on the number of intratumoral vessels and response to cytotoxic anticancer therapies was assessed in animals bearing the Lewis lung carcinoma. Treatment with each of the antiangiogenic agents alone and in two agent combinations decreased the number of intratumoral vessels visualized by CD31 or Factor VIII staining to 30% to 50% of the number in the untreated control tumors. In general, the antiangiogenic agents are more effective adjuvants to cytotoxic therapies when used as two agent combinations than as single agents. The most effective antiangiogenic combinations were: TNP-470/minocycline > TNP-470/genistein > TNP-470/suramin. The increases in the response of the primary tumor to cyclophosphamide, adriamycin, CDDP, BCNU, x-rays or 5-**fluorouracil** and the lung metastases occur to about the same level with the addition of antiangiogenic agents to the therapies. With the treatment combination TNP-470/minocycline/cyclophosphamide 40% of the animals were cured. The results of these studies indicate that antiangiogenic agents can be very useful additions to treatment regimens for solid tumors.

L6 ANSWER 12 OF 22 CANCERLIT  
 AN 97330659 CANCERLIT  
 DN 97330659 PubMed ID: 9187118  
 TI Enhanced antitumor activity of combination radioimmunotherapy (131I-labeled monoclonal antibody A33) with chemotherapy (**fluorouracil**).  
 AU Tschmelitsch J; Barendswaard E; Williams C Jr; Yao T J; Cohen A M; Old L J; Welt S  
 CS New York Branch, Ludwig Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, New York 10021, USA.  
 NC CA-08748 (NCI)  
 SO CANCER RESEARCH, (1997 Jun 1) 57 (11) 2181-6.  
 Journal code: 2984705R. ISSN: 0008-5472.  
 CY United States  
 DT (CLINICAL TRIAL)  
 Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS MEDLINE; Priority Journals  
 OS MEDLINE 97330659  
 EM 199707  
 ED Entered STN: 19970806  
 Last Updated on STN: 19970806  
 AB Monoclonal antibody (mAb) A33 reacts with an antigen expressed by >95% of colon cancer and normal colon epithelial cells. An earlier Phase I trial of 131I-labeled mAb A33 (131I-mAb A33) demonstrated bone marrow suppression as the dose-limiting toxicity, and although modest antitumor effects were seen, no normal colon toxicity was observed. In this study, a nude mouse model was used to test whether combinations of low-dose 131I-mAb A33 (0.1 mCi) and chemotherapy [5-**fluorouracil** (5-FU) or 5-FU + leucovorin, **doxorubicin**, or carmustine] enhance the

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NEWS	22	Aug 26	Sequence searching in REGISTRY enhanced
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NEWS	26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS	27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
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Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>  
Uploading 10031371-2.str

L1 STRUCTURE UPLOADED

=> d l1  
L1 HAS NO ANSWERS  
L1 STR

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss sam  
SAMPLE SEARCH INITIATED 14:48:47 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED - 2 TO ITERATE

100.0% PROCESSED	2 ITERATIONS	1 ANSWERS
SEARCH TIME: 00.00.01		

FULL FILE PROJECTIONS:	ONLINE	**COMPLETE**
	BATCH	**COMPLETE**
PROJECTED ITERATIONS:	2 TO	124

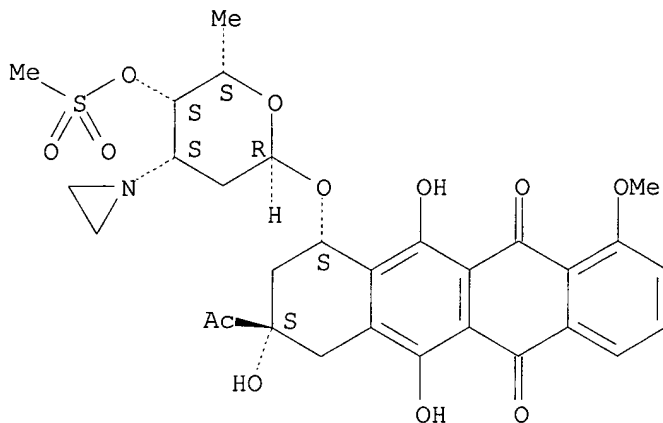
PROJECTED ANSWERS: 1 TO 80

L2 1 SEA SSS SAM L1

=> d scan

L2 1 ANSWERS REGISTRY COPYRIGHT 2002 ACS  
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MF C30 H33 N O12 S

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

ALL ANSWERS HAVE BEEN SCANNED

=> s l1 sss full  
FULL SEARCH INITIATED 14:49:03 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 26 TO ITERATE

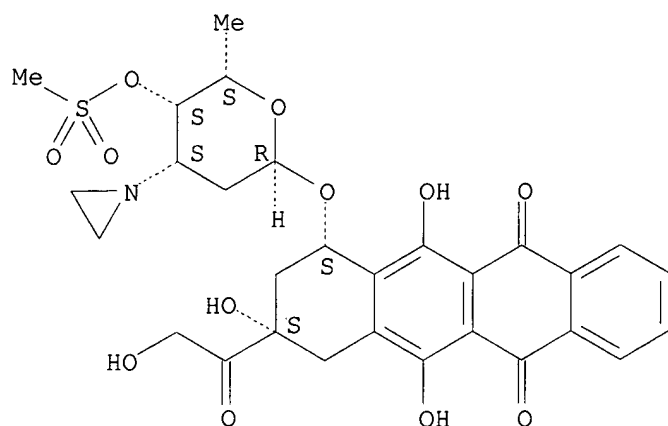
100.0% PROCESSED 26 ITERATIONS 5 ANSWERS  
SEARCH TIME: 00.00.03

L3 5 SEA SSS FUL L1

=> d scan

L3 5 ANSWERS REGISTRY COPYRIGHT 2002 ACS  
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MF C29 H31 N O12 S

Absolute stereochemistry.

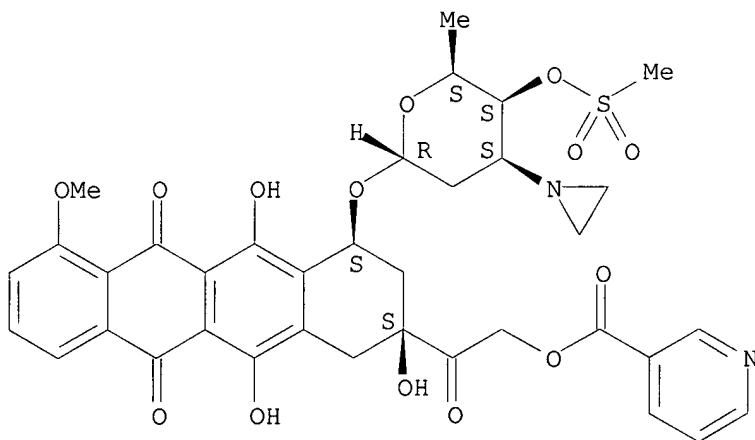


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 5 ANSWERS REGISTRY COPYRIGHT 2002 ACS  
 IN 3-Pyridinecarboxylic acid, 2-[4-[[3-(1-aziridiny)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]-2-oxoethyl ester, (2S-cis)- (9CI)  
 MF C36 H36 N2 O14 S

Absolute stereochemistry.

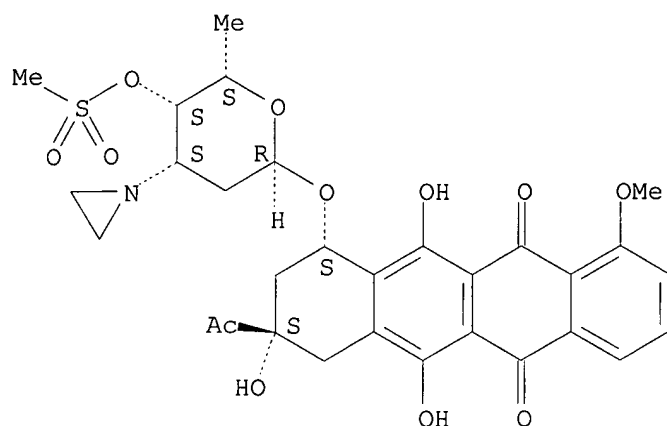


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 5 ANSWERS REGISTRY COPYRIGHT 2002 ACS  
 IN 5,12-Naphthacenedione, 8-acetyl-10-[[3-(1-aziridiny)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)- (9CI)  
 MF C30 H33 N O12 S

Absolute stereochemistry.

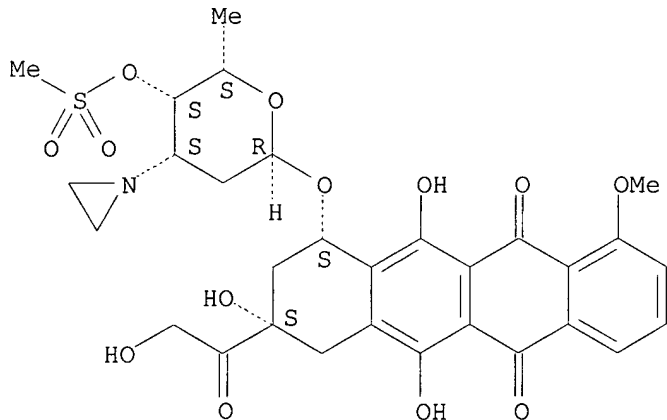


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 5 ANSWERS REGISTRY COPYRIGHT 2002 ACS  
 IN 5,12-Naphthacenedione, 10-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S-cis)- (9CI)  
 MF C30 H33 N O13 S

Absolute stereochemistry.

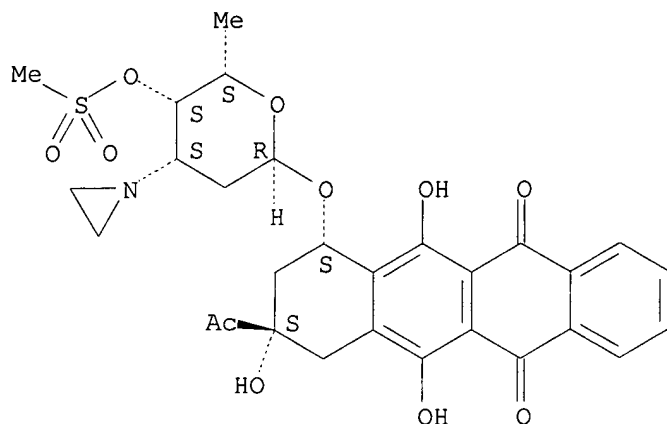


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 5 ANSWERS REGISTRY COPYRIGHT 2002 ACS  
 IN 5,12-Naphthacenedione, 9-acetyl-7-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI)  
 MF C29 H31 N O11 S

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

ALL ANSWERS HAVE BEEN SCANNED

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

141.04

141.25

FILE 'CAPLUS' ENTERED AT 14:49:42 ON 27 NOV 2002

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FILE COVERS 1907 - 27 Nov 2002 VOL 137 ISS 22

FILE LAST UPDATED: 26 Nov 2002 (20021126/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s 13/THU and antimetbolite and fluorouracil and gemcitabine and tumor and synerg? and antineoplastic and fluoropyrimidine and angiogenesis

17 L3

477649 THU/RL

14 L3/THU

(L3 (L) THU/RL)

0 ANTIMETBOLITE

13659 FLUOROURACIL

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    268 FLUOROURACILS
13672 FLUOROURACIL
      (FLUOROURACIL OR FLUOROURACILS)
    1244 GEMCITABINE
265654 TUMOR
111364 TUMORS
303054 TUMOR
      (TUMOR OR TUMORS)
    83039 SYNERG?
    8615 ANTINEOPLASTIC
    374 ANTINEOPLASTICS
    8779 ANTINEOPLASTIC
      (ANTINEOPLASTIC OR ANTINEOPLASTICS)
    826 FLUOROPYRIMIDINE
    470 FLUOROPYRIMIDINES
    1017 FLUOROPYRIMIDINE
      (FLUOROPYRIMIDINE OR FLUOROPYRIMIDINES)
15233 ANGIOGENESIS
L4      0 L3/THU AND ANTIMETABOLITE AND FLUOROURACIL AND GEMCITABINE AND
      TUMOR AND SYNERG? AND ANTINEOPLASTIC AND FLUOROPYRIMIDINE AND
      ANGIOGENESIS

=> s l3/THU and antimetabolite and fluorouracil and gemcitabine and tumor and
synerg? and antineoplastic and fluoropyrimidine and angiogenesis
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477649 THU/RL
    14 L3/THU
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    13659 FLUOROURACIL
    268 FLUOROURACILS
    13672 FLUOROURACIL
      (FLUOROURACIL OR FLUOROURACILS)
    1244 GEMCITABINE
265654 TUMOR
111364 TUMORS
303054 TUMOR
      (TUMOR OR TUMORS)
    83039 SYNERG?
    8615 ANTINEOPLASTIC
    374 ANTINEOPLASTICS
    8779 ANTINEOPLASTIC
      (ANTINEOPLASTIC OR ANTINEOPLASTICS)
    826 FLUOROPYRIMIDINE
    470 FLUOROPYRIMIDINES
    1017 FLUOROPYRIMIDINE
      (FLUOROPYRIMIDINE OR FLUOROPYRIMIDINES)
15233 ANGIOGENESIS
L5      0 L3/THU AND ANTIMETABOLITE AND FLUOROURACIL AND GEMCITABINE AND
      TUMOR AND SYNERG? AND ANTINEOPLASTIC AND FLUOROPYRIMIDINE AND
      ANGIOGENESIS

=> s l3/THU
    17 L3
477649 THU/RL
L6      14 L3/THU
      (L3 (L) THU/RL)

=> s l6 and tumor
    265654 TUMOR
    111364 TUMORS

```

303054 TUMOR  
(TUMOR OR TUMORS)

L7 10 L6 AND TUMOR

=> s 17 and 5-fluoropyrimidine or gemcitabine or 5-fluoropyrimidine and synergistic

5298256 5  
826 FLUOROPYRIMIDINE  
470 FLUOROPYRIMIDINES  
1017 FLUOROPYRIMIDINE  
(FLUOROPYRIMIDINE OR FLUOROPYRIMIDINES)  
240 5-FLUOROPYRIMIDINE  
(5(W) FLUOROPYRIMIDINE)  
1244 GEMCITABINE  
5298256 5  
826 FLUOROPYRIMIDINE  
470 FLUOROPYRIMIDINES  
1017 FLUOROPYRIMIDINE  
(FLUOROPYRIMIDINE OR FLUOROPYRIMIDINES)  
240 5-FLUOROPYRIMIDINE  
(5(W) FLUOROPYRIMIDINE)  
52497 SYNERGISTIC  
47 SYNERGISTICS  
52527 SYNERGISTIC  
(SYNERGISTIC OR SYNERGISTICS)

L8 1253 L7 AND 5-FLUOROPYRIMIDINE OR GEMCITABINE OR 5-FLUOROPYRIMIDINE  
AND SYNERGISTIC

=> dis 17 1-7 ibib abs hitstr

L7 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:693333 CAPLUS

DOCUMENT NUMBER: 135:262228

TITLE: Crystalline alkycycline derivative

INVENTOR(S): Tomasi, Attilio; Ungari, Mario; Galli, Mauro;  
Fumagalli, Paolo

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 13 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

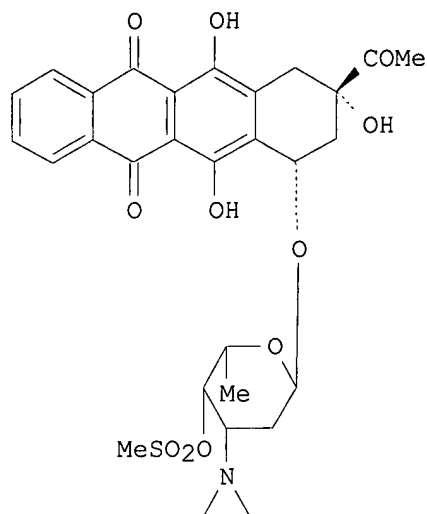
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068661	A2	20010920	WO 2001-EP2783	20010312
WO 2001068661	A3	20020321		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,  
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,  
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,  
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2000-6601 A 20000317

GI



I

AB The cryst. form of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (I) is prepd. for use in the prepn. of pharmaceutical compns. for the treatment of **tumors**. Cryst. I was prepd. from amorphous I using Et acetate and THF for crystn.

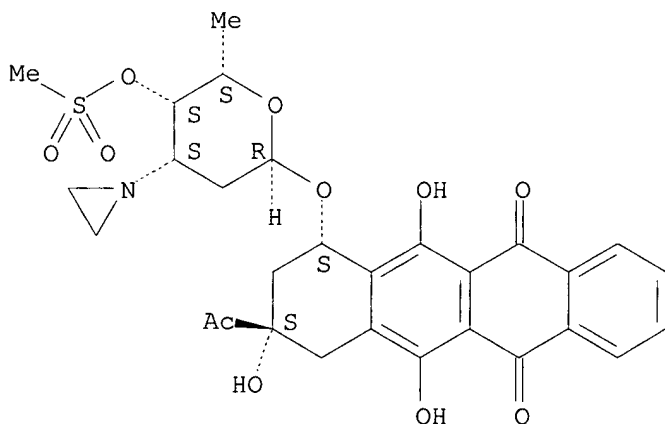
IT **171047-47-5**

RL: PEP (Physical, engineering or chemical process); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)  
(cryst. alkycycline deriv.)

RN 171047-47-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:380379 CAPLUS

DOCUMENT NUMBER: 134:371802

TITLE: Lipid complex of alkycyclines as antitumor agents

INVENTOR(S): Cherian, Mathew; Bianchi Carnevale, Claudia; Colajori, Elena; Valota, Olga

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 17 pp.

CODEN: PIXXD2



DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001035937	A2	20010525	WO 2000-EP10997	20001030
WO 2001035937	A3	20011220		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1227795	A2	20020807	EP 2000-979540	20001030
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			

PRIORITY APPLN. INFO.: GB 1999-26843 A 19991112  
WO 2000-EP10997 W 20001030

AB An antitumor pharmaceutical compn. comprising a liophilizate of a water insol. alkycycline, a phospholipid, a buffer and a pharmaceutically acceptable lyophilization excipient. The compn. is highly stable and exerts a strong antitumor activity without substantially inducing side effects. Thus, 5 g of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin was dissolved in 100 mL of methylene chloride. To this soln. was added 95g of dimyristoylphosphatidyl choline, 30 g of dimyristoylphosphatidyl glycerol, and 40 g of cholesterol dissolved in 1.7 L of methylene chloride and stirred. To the above soln. was added 4.61 g of phosphate buffer at a pH = 8.5. The two-phase system was stirred using a lab. stirrer and then sparged with nitrogen till the level of methylene chloride was less than 1%. To this soln. was added a soln. of mannitol and the suspension was then homogenized and freeze dried. The freeze-dried product was stable after 18 mo of storage at -20.degree. and +5.degree., and the product still had over 90% of its initial potency. Efficacy of the compn. in the treatment of patients with solid tumors was shown.

IT 171047-47-5

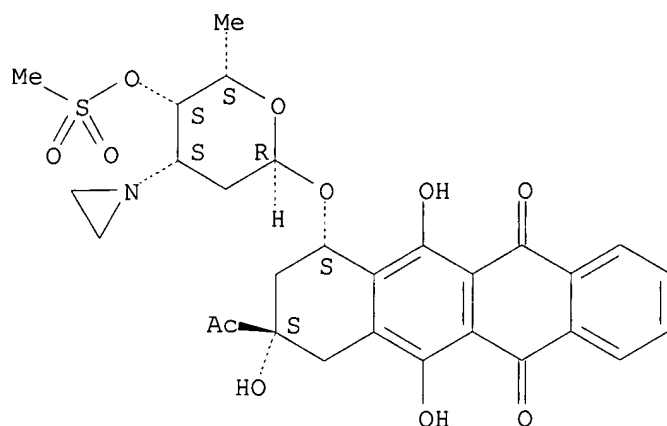
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(lipid complex of alkycyclines as antitumor agents)

RN 171047-47-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:227312 CAPLUS

DOCUMENT NUMBER: 135:14016

TITLE: 4-Demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulphonyl-daunorubicin (PNU-159548), a novel anticancer agent active against tumor cell lines with different resistance mechanisms

AUTHOR(S): Marchini, Sergio; Damia, Giovanna; Broggini, Massimo; Pennella, Giulia; Ripamonti, Marina; Marsiglio, Aurelio; Geroni, Cristina

CORPORATE SOURCE: Lab. Mol. Pharmacol., Istituto di Ricerche Farmacologiche "Mario Negri", Milan, 20157, Italy

SOURCE: Cancer Research (2001), 61(5), 1991-1995  
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The activity of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyl-daunorubicin (PNU-159548), a new alkycycline with high antitumor activity against a broad range of cancer cells, was evaluated in vitro and in vivo in cells selected for resistance to different anticancer agents. Both in vitro and in vivo, PNU-159548 did retain its activity in cells expressing the multidrug resistance (MDR) phenotype, assocd. to MDR-1 gene overexpression or with an alteration in the topoisomerase II gene (altered MDR), independently on the drug used for the selection of the resistant cell line. According to these data, the intracellular uptake of PNU-159548 is not influenced by the presence of MDR-1. PNU-159548 was also active, both in vitro and in vivo, against cells showing resistance to various alkylating agents (including cisplatin, cyclophosphamide, and melphalan) and topoisomerase I-inhibitors. Cells defective in nucleotide excision repair, which did show hypersensitivity to treatment with UV irradiation and alkylating agents, showed only a marginally increased sensitivity to PNU-159548. Similarly, the activity of the drug was not influenced by the mismatch repair system, as assessed in two different cellular systems deficient in hMLH1 expression and in which hMLH1 activity was restored by chromosome 3 transfer. The results obtained clearly indicate that the new anticancer agent PNU-159548 is able to overcome the classical mechanisms of resistance emerging after treatment with the most clinically used anticancer agents, and it could represent an alternate choice in the treatment of those tumors refractory to conventional therapy.

IT 171047-47-5, PNU-159548

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

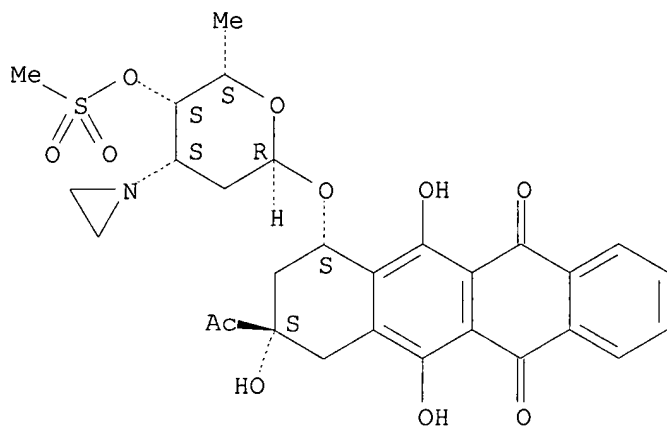
(anticancer agent PNU-159548 is active against tumor cell

lines with different resistance mechanisms)

RN 171047-47-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:227311 CAPLUS

DOCUMENT NUMBER: 135:28784

TITLE: Pharmacological and toxicological aspects of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulphonyl-daunorubicin (PNU-159548): a novel antineoplastic agent

AUTHOR(S): Geroni, Cristina; Ripamonti, Marina; Arrigoni, Claudio; Fiorentini, Francesco; Capolongo, Laura; Moneta, Donatella; Marchini, Sergio; Della Torre, Paola; Albanese, Clara; Lamparelli, Maria Grazia; Ciomei, Marina; Rossi, Rosaria; Caruso, Michele

CORPORATE SOURCE: Department of Pharmacology, Pharmacia Corporation, Milan, 20014, Italy

SOURCE: Cancer Research (2001), 61(5), 1983-1990  
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 4-Demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyl-daunorubicin (PNU-159548) belongs to a novel class of antitumor compds. (termed alkylcyclines) and is currently undergoing Phase II clin. trial. In the present study, the authors investigated the in vitro and in vivo antitumor activity, the pharmacokinetics, and the toxicol. profile of this compd. PNU-159548 showed good cytotoxic activity in murine and human cancer cells growing in vitro, with an av. concn. for 50% growth inhibition of 15.8 ng/mL. The drug showed strong antitumor efficacy in vivo after i.v. and p.o. administration against rapidly proliferating murine leukemias and slowly growing transplantable human xenografts. At nontoxic doses, PNU-159548 produced complete regression and cures in ovarian, breast, and human small cell lung carcinomas. 14 Of 16 models studied, including colon, pancreatic, gastric, and renal carcinomas, astrocytoma and melanoma, were found to be sensitive to PNU-159548. In addn., PNU-159548 was effective against intracranially implanted tumors. Toxicol. studies revealed myelosuppression as the main toxicity in both mice and dogs. The max. tolerated doses, after a single administration, were 2.5

mg/kg of body wt. in mice, 1.6 mg/kg in rats, and 0.3 mg/kg in dogs. In the cyclic studies, the max. tolerated doses were 0.18 mg/kg/day (cumulative dose/cycle: 0.54 mg/kg) in rats and 0.05 mg/kg/day (cumulative dose/cycle: 0.15 mg/kg) in dogs. PNU-159548 showed minimal cardiotoxicity, when compared with doxorubicin in the chronic rat model at a dose level inducing similar myelotoxicity. Animal pharmacokinetics, carried out in mice, rats, and dogs, was characterized by high vols. of distribution, blood plasma clearance of the same order of the hepatic blood flow, and short terminal half-life. These findings support the conclusion that PNU-159548 is an excellent candidate for clin. trials in the treatment of cancer.

IT 171047-47-5, PNU-159548

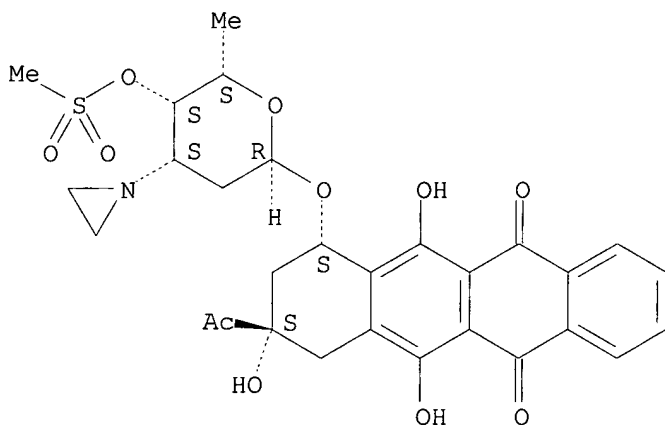
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)

(pharmacol. and toxicol. aspects of PNU-159548, a novel antineoplastic agent)

RN 171047-47-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:63847 CAPLUS

DOCUMENT NUMBER: 134:136690

TITLE: Combination daunorubicin derivative and recombinant human anti-HER2 antibody antitumor agents

INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia and Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 9 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

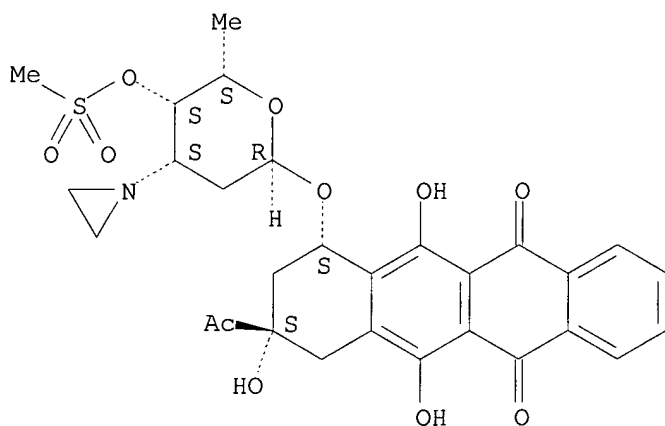
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005425	A2	20010125	WO 2000-EP6540	20000710
WO 2001005425	A3	20010517		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
 EP 1200098 A2 20020502 EP 2000-945903 20000710  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL  
 PRIORITY APPLN. INFO.: GB 1999-17012 A 19990720  
 WO 2000-EP6540 W 20000710  
 GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The combined use of I or II and a recombinant humanized anti-HER2 antibody, preferably trastuzumab, in the treatment of **tumors** and the use of said combination in the treatment and/or prevention of **tumor** metastasis is provided.  
 IT **171047-47-5**  
 RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses) (combination daunorubicin deriv. and recombinant human anti-HER2 antibody antitumor agents)  
 RN 171047-47-5 CAPLUS  
 CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2001:63809 CAPLUS  
 DOCUMENT NUMBER: 134:110448  
 TITLE: Synergistic composition comprising daunorubicin derivatives and antimetabolite compounds  
 INVENTOR(S): Geroni, Maria Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino  
 PATENT ASSIGNEE(S): Pharmacia and Upjohn S.p.A., Italy  
 SOURCE: PCT Int. Appl., 12 pp.  
 CODEN: PIXXD2

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

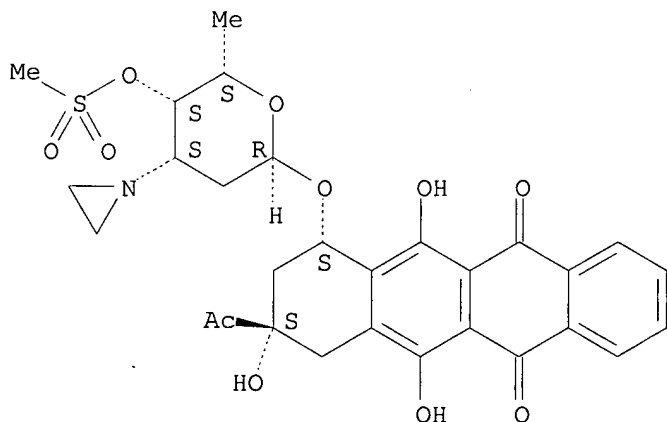
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005382	A1	20010125	WO 2000-EP6545	20000710
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1200099	A1	20020502	EP 2000-949297	20000710
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: GB 1999-16882 A 19990719  
 WO 2000-EP6545 W 20000710

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an antimetabolite compd. in the treatment of **tumors**, esp. in the treatment or prevention of metastasis or in the treatment of **tumors** by the inhibition of angiogenesis is described. Thus, at a dose of 15 and 60 mg/kg of gemcitabine alone (i.p. day 1 after **tumor** injection), PNU 159548 alone (i.v. day 1 after **tumor** injection, administered 2 after gemcitabine), were assocd., without toxicity, with ILS% values of 50 and 83 and 33 and 67, resp. By combining gemcitabine and PNU 159548 at the same doses and with the same schedule, an increase of activity with ILS% values of 117 and 204 were obsd., indicating a synergistic effect as shown by the combination index (CI) of 1.4 and 1.3, resp.

IT **171047-47-5**, PNU 159548  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)  
 (synergistic compn. comprising daunorubicin derivs. and antimetabolite compds.)  
 RN 171047-47-5 CAPLUS  
 CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:824131 CAPLUS

DOCUMENT NUMBER: 134:508

TITLE: Combined method of treatment comprising an aromatase inhibitor and a further biologically active compound

INVENTOR(S): Di Salle, Enrico; Zaccheo, Tiziana; Tedeschi, Michele

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 26 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069467	A1	20001123	WO 2000-EP3407	20000414
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1178831	A1	20020213	EP 2000-917084	20000414
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			

PRIORITY APPLN. INFO.: GB 1999-11582 A 19990518  
WO 2000-EP3407 W 20000414

AB A compn. for use in breast cancer therapy in humans comprising, in amts. effective to produce a superadditive antitumor effect: (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent. The combination of exemestane and epirubicin on DMBA-induced mammary tumors in rats was more effective than either compd. alone.

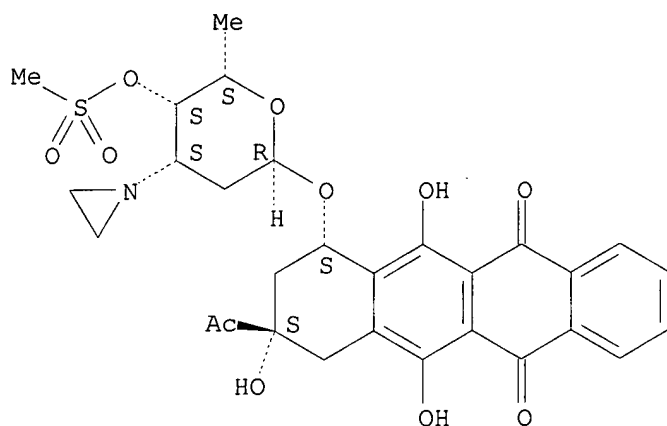
IT 171047-47-5, PNU 159548

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(antitumor agent-aromatase inhibitor combinations)

RN 171047-47-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file medline  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
77.00	218.25

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-4.34	-4.34

CA SUBSCRIBER PRICE

FILE 'MEDLINE' ENTERED AT 14:55:33 ON 27 NOV 2002

FILE LAST UPDATED: 23 NOV 2002 (20021123/UP). FILE COVERS 1958 TO DATE.

On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

If you received SDI results from MEDLINE on October 8, 2002, these may have included old POPLINE data and in some cases duplicate abstracts. For further information on this situation, please visit NLM at:  
[http://www.nlm.nih.gov/pubs/techbull/so02/so02\\_popline.html](http://www.nlm.nih.gov/pubs/techbull/so02/so02_popline.html)

To correct this problem, CAS will remove the POPLINE records from the MEDLINE file and process the SDI run dated October 8, 2002 again.

Customers who received SDI results via email or hard copy prints on October 8, 2002 will not be charged for this SDI run. If you received your update online and displayed answers, you may request a credit by contacting the CAS Help Desk at 1-800-848-6533 in North America or 614-447-3698 worldwide, or via email to [help@cas.org](mailto:help@cas.org)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 13

L9 0 L3

=> file embase  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.86	219.11

FULL ESTIMATED COST



DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-4.34

FILE 'EMBASE' ENTERED AT 14:56:39 ON 27 NOV 2002  
 COPYRIGHT (C) 2002 Elsevier Science B.V. All rights reserved.

FILE COVERS 1974 TO 21 Nov 2002 (20021121/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3  
 L10 0 L3

=> file cancerlit		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	1.21	220.32

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-4.34

FILE 'CANCERLIT' ENTERED AT 14:56:51 ON 27 NOV 2002

FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3  
 L11 0 L3

=> file biosis		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	0.46	220.78

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-4.34

FILE 'BIOSIS' ENTERED AT 14:57:02 ON 27 NOV 2002  
 COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC.(R)

FILE COVERS 1969 TO DATE.  
 CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT  
 FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 20 November 2002 (20021120/ED)

=> s l3  
 L12 9 L3

=> dis l12 1-9 ibib abs hitstr

'HITSTR' IS NOT A VALID FORMAT FOR FILE 'BIOSIS'

The following are valid formats:

The default display format is BIB.

ABS ----- AB  
ALL ----- AN, DN, TI, AU, CS, PI, SO, NTE, DT, FS, LA, SL, AB,  
                  NCL, CC, BC, IT (CT, ST), CO, NA, GT, ORGN, RN, CN, GEN  
BIB ----- AN, DN, TI, AU, CS, PI, SO, NTE, DT, FS, LA, SL  
CBIB ----- AN, compressed bibliographic information  
DALL ----- ALL, delimited for post-processing  
IABS ----- ABS, with text label  
IALL ----- ALL, indented with text labels  
IBIB ----- BIB, indented with text labels  
IIND ----- IND, indented with text labels  
IND ----- NCL, CC, BC, IT (CT, ST), CO, NA, GT, ORGN, RN, CN, GEN  
HIT ----- all fields containing hit search terms  
HITIND ----- IND  
KWIC ----- Hit terms plus 20 words on either side  
OCC ----- number of occurrences of hit terms and fields  
                  in which they occur

Hit terms will be highlighted in all available fields except MY and PY.

To display a particular field or fields, enter the display field codes. For a list of display field codes, enter 'HELP DFIELDS' at an arrow prompt (=>). Examples of formats include: 'BIB'; 'AB'; 'SO,ST'. You may specify the format fields in any order, and the information will be displayed in the same order as the format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be used with the DISPLAY ACC command to display the record for a specified Accession Number.

ENTER DISPLAY FORMAT (BIB):end

=> dis 12 1-9 bib abs

9 ANSWERS ARE AVAILABLE. SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE

The answer numbers requested are not in the answer set.

ENTER ANSWER NUMBER OR RANGE (1):end

=> dis 112 1-9 bib abs

L112 ANSWER 1 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 2002:440099 BIOSIS  
DN PREV200200440099  
TI Synthesis of PNU-159548 labelled with 14C and 2H.  
AU Felicini, C. (1); Fontana, E.  
CS (1) Global Drug Metabolism Department, Pharmacia, viale Pasteur 10, 20014, Nerviano (MI): chiara.felicini@Pharmacia.com Italy  
SO Journal of Labelled Compounds and Radiopharmaceuticals, (June, 2002) Vol. 45, No. 7, pp. 543-550. <http://www.interscience.wiley.com/jpages/0362-4803>. print.  
ISSN: 0362-4803.  
DT Article  
LA English  
AB The cytotoxic antitumor compound PNU-159548 (1) has been labelled with 14C and 2H. A three-step sequence starting from (14-14C)idarubicin (2a) led to radiochemically pure (> 98%) (14-14C)PNU-159548 with a specific activity of 1.13 GBq/mmol. The synthesis of (2H4)PNU-159548 was carried out in a similar manner starting from (1,1,2,2-2H4)2-bromoethanol (3b).

L12 ANSWER 2 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AN 2002:367387 BIOSIS  
 DN PREV200200367387  
 TI Effectiveness of the novel anticancer agent 4-demetoxy-3'-aziridinyl-4'-methylsulphonyl-daunorubicin (PNU-159548) on human osteosarcoma cells.  
 AU Serra, Massimo (1); Branchat, Gemma Reverter; Incaprera, Marina; Scotlandi, Katia; Manara, Maria Cristina; Benini, Stefania; Geroni, Cristina; Picci, Piero  
 CS (1) Lab. Ricerca Oncologica, Istituti Ortopedici Rizzoli, Bologna Italy  
 SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 57. print.  
 Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002  
 ISSN: 0197-016X.  
 DT Conference  
 LA English

L12 ANSWER 3 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
 AN 2001:262796 BIOSIS  
 DN PREV200100262796  
 TI PNU-159548, a novel cytotoxic antitumor agent with a low cardiotoxic potential.  
 AU Della Torre, Paola; Podesta, Arturo; Imondi, Anthony R. (1); Moneta, Donatella; Sammartini, Umberto; Arrigoni, Claudio; Terron, Andrea; Brughera, Marco  
 CS (1) Battelle, 505 King Avenue, Columbus, OH, 43201-2693 USA  
 SO Cancer Chemotherapy and Pharmacology, (April, 2001) Vol. 47, No. 4, pp. 355-360. print.  
 ISSN: 0344-5704.  
 DT Article  
 LA English  
 SL English  
 AB Purpose: PNU-159548 (4-demethoxy-3'-deamino-3'aziridinyl-4'-methylsulphonyl-daunorubicin), a derivative of the anticancer idarubicin, has a broad spectrum of antitumoral activity in vitro and in vivo attributable to its DNA intercalating and alkylating properties. The present study was conducted to determine the cardiotoxic activity of PNU-159548 relative to doxorubicin in a chronic rat model sensitive to anthracycline-induced cardiomyopathy. Methods: Young adult male rats were allocated to the following treatment groups: group 1, PNU-159548 vehicle control (colloidal dispersion); group 2, doxorubicin control (saline); groups 3, 4, 5, 6, and 7, PNU-159548 at 0.12, 0.25, 0.50, 0.75, and 1.0 mg/kg, respectively; and group 8, 1.0 mg/kg doxorubicin. Treatments were administered intravenously once weekly for 4 weeks (first sacrifice time) or for 7 weeks (rats killed at weeks 8, 12, 22, 27, or 35). Body weights, organ weights, serum chemistry, hematology, serum troponin-T, and cardiac histopathology were followed throughout the study. Results: Doxorubicin caused irreversible cardiomyopathy evident at week 4 in some rats and progressing in severity in all rats by week 8. There were also marked myelotoxicity, increased liver and kidney weights, testicular atrophy, and about 20% mortality by week 27 in doxorubicin-treated rats. The deaths were attributed to cardiomyopathy and/or nephropathy. PNU-159548 caused a dose-dependent myelotoxicity, with the dose of 0.5 mg/kg per week being equimyelotoxic to 1.0 mg/kg per week doxorubicin. PNU-159548 also caused an increase in liver weight that was reversible and a non-reversible testicular atrophy but, unlike doxorubicin, had no effect on kidney weight. At equimyelotoxic doses, the cardiotoxicity caused by PNU-159548, expressed as the mean total score, was less than one-twentieth of that induced by doxorubicin, and much less than that predicted on the basis of its content of idarubicin, which is in turn markedly less cardiotoxic than doxorubicin. Conclusions: The novel cytotoxic antitumor derivative, PNU-159548, is significantly less cardiotoxic than doxorubicin at equimyelosuppressive doses. The combination of intercalating and alkylating activities within the same molecule without the cardiotoxic

side effects of anthracyclines makes PNU-159548 an excellent candidate for clinical development in oncology.

- L12 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 2001:184777 BIOSIS  
DN PREV200100184777  
TI 4-Demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulphonyl-daunorubicin (PNU-159548), a novel anticancer agent active against tumor cell lines with different resistance mechanisms.  
AU Marchini, Sergio (1); Damia, Giovanna; Brogginì, Massimo; Pennella, Giulia; Ripamonti, Marina; Marsiglio, Aurelio; Geroni, Cristina  
CS (1) Laboratory of Molecular Pharmacology, Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea 62, 20157, Milan: marchini@marionegri.it Italy  
SO Cancer Research, (March 1, 2001) Vol. 61, No. 5, pp. 1991-1995. print. ISSN: 0008-5472.  
DT Article  
LA English  
SL English  
AB The activity of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulphonyl-daunorubicin (PNU-159548), a new alkylcycline with high antitumor activity against a broad range of cancer cells, was evaluated in vitro and in vivo in cells selected for resistance to different anticancer agents. Both in vitro and in vivo, PNU-159548 did retain its activity in cells expressing the multidrug resistance (MDR) phenotype, associated to MDR-1 gene overexpression or with an alteration in the topoisomerase II gene (altered MDR), independently on the drug used for the selection of the resistant cell line. According to these data, the intracellular uptake of PNU-159548 is not influenced by the presence of MDR-1. PNU-159548 was also active, both in vitro and in vivo, against cells showing resistance to various alkylating agents (including cisplatin, cyclophosphamide, and melphalan) and topoisomerase I-inhibitors. Cells defective in nucleotide excision repair, which did show hypersensitivity to treatment with UV irradiation and alkylating agents, showed only a marginally increased sensitivity to PNU-159548. Similarly, the activity of the drug was not influenced by the mismatch repair system, as assessed in two different cellular systems deficient in hMLH1 expression and in which hMLH1 activity was restored by chromosome 3 transfer. The results obtained clearly indicate that the new anticancer agent PNU-159548 is able to overcome the classical mechanisms of resistance emerging after treatment with the most clinically used anticancer agents, and it could represent an alternate choice in the treatment of those tumors refractory to conventional therapy.
- L12 ANSWER 5 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 2001:184776 BIOSIS  
DN PREV200100184776  
TI Pharmacological and toxicological aspects of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulphonyl-daunorubicin (PNU-159548): A novel antineoplastic agent.  
AU Geroni, Cristina (1); Ripamonti, Marina; Arrigoni, Claudio; Fiorentini, Francesco; Capolongo, Laura; Moneta, Donatella; Marchini, Sergio; Della Torre, Paola; Albanese, Clara; Lamparelli, Maria Grazia; Ciomei, Marina; Rossi, Rosaria; Caruso, Michele  
CS (1) Pharmacology Department, Discovery Research Oncology, Pharmacia Corporation, Viale Pasteur 10, 20014, Nerviano, Milan: cristina.geroni@eu.pnu.com Italy  
SO Cancer Research, (March 1, 2001) Vol. 61, No. 5, pp. 1983-1990. print. ISSN: 0008-5472.  
DT Article  
LA English  
SL English  
AB 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulphonyl-daunorubicin (PNU-159548) belongs to a novel class of antitumor compounds (termed alkylcycelines) and is currently undergoing Phase II clinical trial. In the

present study, we investigated the in vitro and in vivo antitumor activity, the pharmacokinetics, and the toxicological profile of this compound. PNU-159548 showed good cytotoxic activity in murine and human cancer cells growing in vitro, with an average concentration for 50% growth inhibition of 15.8 ng/ml. The drug showed strong antitumor efficacy in vivo after i.v. and p.o. administration against rapidly proliferating murine leukemias and slowly growing transplantable human xenografts. At nontoxic doses, PNU-159548 produced complete regression and cures in ovarian, breast, and human small cell lung carcinomas. Fourteen of 16 models studied, including colon, pancreatic, gastric, and renal carcinomas, astrocytoma and melanoma, were found to be sensitive to PNU-159548. In addition, PNU-159548 was effective against intracranially implanted tumors. Toxicological studies revealed myelosuppression as the main toxicity in both mice and dogs. The maximum tolerated doses, after a single administration, were 2.5 mg/kg of body weight in mice, 1.6 mg/kg in rats, and 0.3 mg/kg in dogs. In the cyclic studies, the maximum tolerated doses were 0.18 mg/kg/day (cumulative dose/cycle: 0.54 mg/kg) in rats and 0.05 mg/kg/day (cumulative dose/cycle: 0.15 mg/kg) in dogs. PNU-159548 showed minimal cardiotoxicity, when compared with doxorubicin in the chronic rat model at a dose level inducing similar myelotoxicity. Animal pharmacokinetics, carried out in mice, rats, and dogs, was characterized by high volumes of distribution, plasma clearance of the same order of the hepatic blood flow, and short terminal half-life. These findings support the conclusion that PNU-159548 is an excellent candidate for clinical trials in the treatment of cancer.

- L12 ANSWER 6 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 2001:45126 BIOSIS  
DN PREV200100045126  
TI PNU-159548: A novel cytotoxic antitumor agent with a low cardiotoxic potential.  
AU Della Torre, P. (1); Podesta, A. (1); Terron, A. (1); Geroni, C. (1); Brughera, M. (1)  
CS (1) Oncology, Pharmacia Corporation, Nerviano, MI Italy  
SO Tumori, (July August, 2000) Vol. 86, No. 4 Suppl. 1, pp. 84. print.  
Meeting Info.: XV Congress of the Italian Cancer Society Turin, Italy  
October 05-07, 2000 Italian Cancer Society  
. ISSN: 0300-8916.  
DT Conference  
LA English  
SL English
- L12 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 2000:235812 BIOSIS  
DN PREV200000235812  
TI Activity of PNU-159548 against repair defective cell lines.  
AU Geroni, Cristina (1); Pennella, Giulia; Broggin, Massimo; Damia, Giovanna; Marchini, Sergio; Ripamonti, Marina  
CS (1) Inst Mario Negri, Milano Italy  
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 425.  
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000  
ISSN: 0197-016X.  
DT Conference  
LA English  
SL English
- L12 ANSWER 8 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
AN 1999:461612 BIOSIS  
DN PREV199900461612  
TI Determination of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulphonyldaunorubicin and its 13-hydroxy metabolite by direct injection of human plasma into a column-switching liquid chromatography

system with mass spectrometric detection.

AU Breda, M. (1); Basileo, G.; Fonte, G.; Long, J.; James, C. A.  
CS (1) Drug Metabolism Research, Pharmacia and Upjohn, Viale Pasteur 10,  
Nerviano, 20014, Milan Italy  
SO Journal of Chromatography A, (Aug. 27, 1999) Vol. 854, No. 1-2, pp. 81-92.  
ISSN: 0021-9673.

DT Article

LA English

SL English

AB A selective, sensitive and fully automated column-switching LC system using direct injection of human plasma followed by mass spectrometry (MS) detection was developed and validated to determine the concentrations of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulphonyldaunorubicin (PNU-159548) and its 13-hydroxy metabolite (PNU-169884). A 50- $\mu$ l human plasma sample was directly introduced into a C4-alkyl-diol silica clean-up column separating analytes from proteins and polar endogenous compounds using water and methanol as the mobile phase. The fraction containing PNU-159548 and its metabolite was back-flushed and transferred to the analytical column. The compounds were separated using a Zorbax SB C8 column (150X4.6 mm, 5  $\mu$ m) under gradient conditions with the mobile phase containing acetonitrile and 2 mM ammonium formate, pH 3.5. MS detection was by atmospheric pressure ionisation with multiple reaction monitoring in positive ion mode. Linearity was demonstrated over the calibration range of 0.051-10.291 ng/ml for PNU-159548 and 0.104-10.434 ng/ml for PNU-169884. The assay was validated with respect to accuracy, precision and analyte stability. On the basis of the validation data, the developed analytical method was found to be suitable for use in Phase I clinical studies.

L12 ANSWER 9 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1996:190843 BIOSIS

DN PREV199698746972

TI Sequence-specific DNA interactions by novel alkylating anthracycline derivatives.

AU Marchini, S.; Gonzalez Paz, O.; Ripamonti, M.; Geroni, C.; Bargiotti, A.; Caruso, M.; Todeschi, S.; D'Incalci, M.; Broggin, M. (1)

CS (1) Ist. Ricerche Farmacol. Mario Negri, via Eritrea 62, 20157 Milan Italy

SO Anti-Cancer Drug Design, (1995) Vol. 10, No. 8, pp. 641-653.

ISSN: 0266-9536.

DT Article

LA English

AB New alkylating anthracycline derivatives with promising antitumor activity have been synthesized. We selected two of these compounds, 4-demethoxy-N,N-bis (2 chloroethyl)-4'-methylsulfonyl-daunorubicin (FCE 27726) and 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyl daunorubicin (FCE 28729), comparing their interaction with DNA and that of the non-alkylating derivative 4-demethoxy-4'-methylsulfonyl-daunorubicin (FCE 27894). The two alkylating derivatives were more cytotoxic than idarubicin and presented low cross-resistance with doxorubicin. Both FCE 27726 and FCE 28729 were found to alkylate guanines at the N-7 position in the major groove with roughly the same specificity, but at different concentrations. FCE 27726 was 10 times more potent than FCE 28729 in alkylating DNA. At higher concentrations, FCE 27726 was able to alkylate adenines, possibly at the N-3 position contained in a sequence 5'-PyAA. FCE 27726, as expected, was able to form DNA interstrand cross-links either in vitro and in vivo in treated cells. FCE 28729 did not form DNA interstrand cross-links in vivo. In vitro, at high concentrations, some DNA interstrand cross-links were evident. The non-alkylating derivative FCE 27894 did not produce any alkylation or DNA interstrand cross-links either in vitro or in vivo.

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NEWS	8	Apr 22	Federal Research in Progress (FEDRIP) now available
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NEWS	13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS	14	Jul 29	Enhanced polymer searching in REGISTRY
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NEWS	16	Aug 08	CANCERLIT reload
NEWS	17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS	18	Aug 08	NTIS has been reloaded and enhanced
NEWS	19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS	20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS	21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS	22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS	23	Sep 03	JAPIO has been reloaded and enhanced
NEWS	24	Sep 16	Experimental properties added to the REGISTRY file
NEWS	25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS	26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS	27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS	28	Oct 21	EVENTLINE has been reloaded
NEWS	29	Oct 24	BEILSTEIN adds new search fields
NEWS	30	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS	31	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS	32	Nov 18	DKILIT has been renamed APOLLIT
NEWS	33	Nov 25	More calculated properties added to REGISTRY
NEWS EXPRESS			October 14 CURRENT WINDOWS VERSION IS V6.01, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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	ENTRY	SESSION
FULL ESTIMATED COST	0.21	0.21

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STRUCTURE FILE UPDATES: 26 NOV 2002 HIGHEST RN 474607-46-0  
DICTIONARY FILE UPDATES: 26 NOV 2002 HIGHEST RN 474607-46-0

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<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>  
Uploading 10031371-1.str

L1 STRUCTURE UPLOADED

=> d l1  
L1 HAS NO ANSWERS  
L1 STR

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

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=> s l1 sss sam  
SAMPLE SEARCH INITIATED 14:36:45 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED - 2 TO ITERATE

100.0% PROCESSED	2 ITERATIONS	1 ANSWERS
SEARCH TIME: 00.00.01		

FULL FILE PROJECTIONS:	ONLINE	**COMPLETE**
	BATCH	**COMPLETE**
PROJECTED ITERATIONS:	2 TO	124



PROJECTED ANSWERS: 1 TO 80

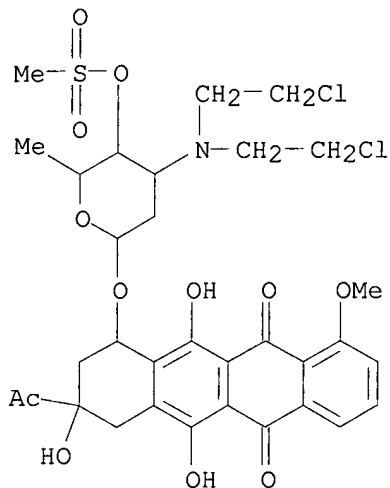
L2 1 SEA SSS SAM L1

=> d scan

L2 1 ANSWERS REGISTRY COPYRIGHT 2002 ACS

IN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)- (9CI)

MF C32 H37 Cl2 N O12 S



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

ALL ANSWERS HAVE BEEN SCANNED

=> s l1 sss full

FULL SEARCH INITIATED 14:37:18 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 42 TO ITERATE

100.0% PROCESSED 42 ITERATIONS

4 ANSWERS

SEARCH TIME: 00.00.01

L3 4 SEA SSS FUL L1

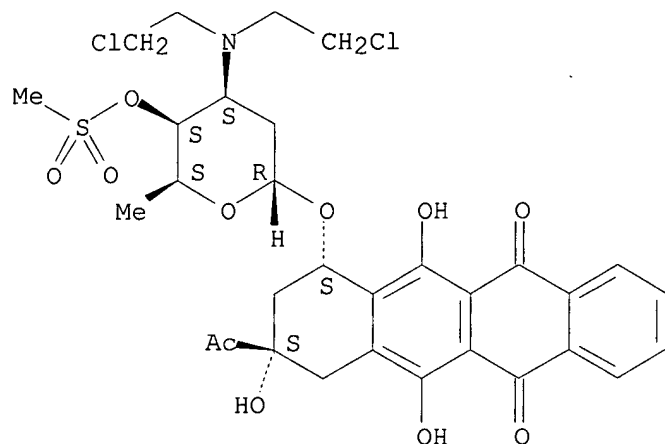
=> d scan

L3 4 ANSWERS REGISTRY COPYRIGHT 2002 ACS

IN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI)

MF C31 H35 Cl2 N O11 S

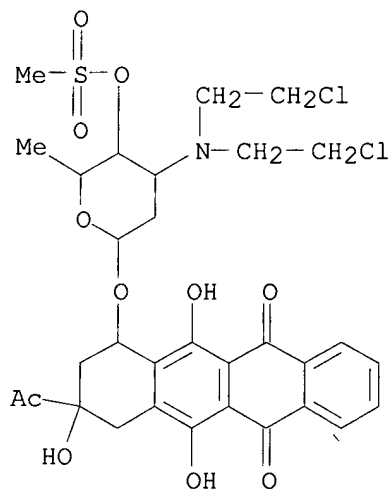
Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

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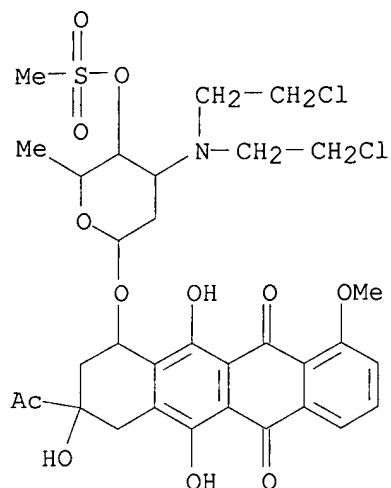
L3 4 ANSWERS REGISTRY COPYRIGHT 2002 ACS  
 IN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-arabino-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S-cis)- (9CI)  
 MF C31 H35 Cl2 N O11 S



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 4 ANSWERS REGISTRY COPYRIGHT 2002 ACS  
 IN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-arabino-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)- (9CI)  
 MF C32 H37 Cl2 N O12 S



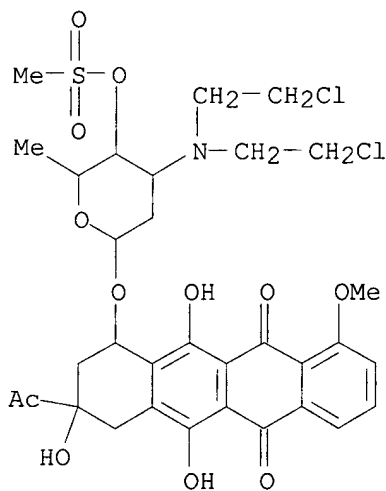
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HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L3 4 ANSWERS REGISTRY COPYRIGHT 2002 ACS

IN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)-(9CI)

MF C32 H37 Cl2 N O12 S



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=> index chemistry  
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141.42	141.63

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INDEX 'AGRICOLA, ALUMINIUM, ANABSTR, APOLLIT, AQUIRE, BABS, BIOCOMMERCE,  
BIOTECHNO, CABA, CAOLD, CAPLUS, CBNB, CEABA-VTB, CEN, CERAB, CIN,  
COMPENDEX, CONFSCI, COPPERLIT, CORROSION, ENCOMPLIT, ENCOMPLIT2, FEDRIP,  
GENBANK, INSPEC, INSPHYS, INVESTEXT, IPA, ...'

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=> s 13  
SUBSTANCE SEARCHES NOT VALID IN INDEX  
Substance searches are not available in index.

=> file caplus  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.53	142.16

FULL ESTIMATED COST

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FILE COVERS 1907 - 27 Nov 2002 VOL 137 ISS 22  
FILE LAST UPDATED: 26 Nov 2002 (20021126/ED)

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=> s 13  
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=> s 13/THU

9 L3  
477649 THU/RL  
L4 7 L3/THU  
(L3 (L) THU/RL)

=> dis 14 1-7 ibib abs

L4 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2001:63847 CAPLUS  
DOCUMENT NUMBER: 134:136690  
TITLE: Combination daunorubicin derivative and recombinant  
human anti-HER2 antibody antitumor agents  
INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele;  
Suarato, Antonino  
PATENT ASSIGNEE(S): Pharmacia and Upjohn S.p.A., Italy  
SOURCE: PCT Int. Appl., 9 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005425	A2	20010125	WO 2000-EP6540	20000710
WO 2001005425	A3	20010517		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1200098	A2	20020502	EP 2000-945903	20000710
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			
PRIORITY APPLN. INFO.:			GB 1999-17012 A 19990720	
			WO 2000-EP6540 W 20000710	

GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The combined use of I or II and a recombinant humanized anti-HER2 antibody, preferably trastuzumab, in the treatment of tumors and the use of said combination in the treatment and/or prevention of tumor metastasis is provided.

L4 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2001:63809 CAPLUS  
DOCUMENT NUMBER: 134:110448  
TITLE: Synergistic composition comprising daunorubicin derivatives and antimetabolite compounds  
INVENTOR(S): Geroni, Maria Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino  
PATENT ASSIGNEE(S): Pharmacia and Upjohn S.p.A., Italy  
SOURCE: PCT Int. Appl., 12 pp.  
CODEN: PIXXD2

DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005382	A1	20010125	WO 2000-EP6545	20000710
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1200099	A1	20020502	EP 2000-949297	20000710
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			

PRIORITY APPLN. INFO.: GB 1999-16882 A 19990719  
WO 2000-EP6545 W 20000710

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an antimetabolite compd. in the treatment of tumors, esp. in the treatment or prevention of metastasis or in the treatment of tumors by the inhibition of angiogenesis is described. Thus, at a dose of 15 and 60 mg/kg of gemcitabine alone (i.p. day 1 after tumor injection), PNU 159548 alone (i.v. day 1 after tumor injection, administered 2 after gemcitabine), were assocd., without toxicity, with ILS% values of 50 and 83 and 33 and 67, resp. By combining gemcitabine and PNU 159548 at the same doses and with the same schedule, an increase of activity with ILS% values of 117 and 204 were obsd., indicating a synergistic effect as shown by the combination index (CI) of 1.4 and 1.3, resp.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:608575 CAPLUS

DOCUMENT NUMBER: 133:187947

TITLE: Antitumor synergistic combination of daunorubicin derivative and an antimitotic

INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.P.A., Italy

SOURCE: PCT Int. Appl., 13 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050033	A2	20000831	WO 2000-EP746	20000131
WO 2000050033	A3	20001221		
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,			

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,  
 CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
 EP 1169035 A2 20020109 EP 2000-904990 20000131  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO  
 BR 2000008454 A 20020129 BR 2000-8454 20000131  
 JP 2002537334 T2 20021105 JP 2000-600644 20000131  
 PRIORITY APPLN. INFO.: GB 1999-4386 A 19990225  
 WO 2000-EP746 W 20000131

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin (I) or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an anti-neoplastic anti-mitotic compd. and/or a platinum deriv. in the treatment of tumors, as well as in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis is disclosed. A dose of 8 mg/kg of oxaliplatin alone (day +3) and a dose of 1 mg/kg I alone (days +1,2) were assocd., without toxicity, with an increase in the lifespan (ILS) values of 83% for both., when the antileukemic activity was detd. in L1210 murine leukemia. Combining oxaliplatin and I at the same doses with the same schedule an increase in the antitumor activity with ILS values of 125% was obsd., indicating a synergistic effect of the combination.

L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:608574 CAPLUS  
 DOCUMENT NUMBER: 133:187946  
 TITLE: Antitumour synergistic combination of daunorubicin derivative and topoisomerase II inhibitor  
 INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino  
 PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy  
 SOURCE: PCT Int. Appl., 13 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050032	A1	20000831	WO 2000-EP745	20000131
W:		AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM		
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EP 1165069	A1	20020102	EP 2000-903657	20000131
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BR 2000008453	A	20020129	BR 2000-8453	20000131
JP 2002537333	T2	20021105	JP 2000-600643	20000131
PRIORITY APPLN. INFO.:			GB 1999-4387 A 19990225	
			WO 2000-EP745 W 20000131	

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin (I) or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an antineoplastic topoisomerase II inhibitor in the treatment of tumors and the use of the combination in the treatment or prevention of metastasis or in the treatment of tumors by inhibition of angiogenesis are disclosed. A dose of 13 mg/kg of doxorubicin alone (day +3) and a dose of 1.5 mg/kg I alone (days +1,2) were assocd., without toxicity, with an increase in the lifespan (ILS)

values of 50 and 67%, resp. Combining doxorubicin at the same doses with the same schedule an increase in the antitumor activity with ILS values of 150% was obsd., indicating a synergistic effect of the combination.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:626051 CAPLUS

DOCUMENT NUMBER: 131:252552

TITLE: Antitumor composition containing a synergistic combination of an anthracycline derivative with a camptothecin derivative

INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 14 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9948503	A1	19990930	WO 1999-EP1897	19990319
W: AU, BG, BR, CA, CN, CZ, HU, ID, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2324610	AA	19990930	CA 1999-2324610	19990319
AU 9933314	A1	19991018	AU 1999-33314	19990319
BR 9908391	A	20001031	BR 1999-8391	19990319
EP 1067941	A1	20010117	EP 1999-914528	19990319
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002507571	T2	20020312	JP 2000-537551	19990319
ZA 9902255	A	19991005	ZA 1999-2255	19990323
NO 2000004703	A	20000920	NO 2000-4703	20000920
US 6403563	B1	20020611	US 2000-646096	20000920

PRIORITY APPLN. INFO.: GB 1998-6324 A 19980324  
WO 1999-EP1897 W 19990319

AB There are provided the combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and an antineoplastic topoisomerase I inhibitor in the treatment of tumors and the use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin in the treatment of brain tumors.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:135051 CAPLUS

DOCUMENT NUMBER: 124:306663

TITLE: Sequence-specific DNA interactions by novel alkylating anthracycline derivatives

AUTHOR(S): Marchini, S.; Gonzalez, O.; Ripamonti, M.; Geroni, C.; Bargiotti, A.; Caruso, M.; Todeschi, S.; D'Incalci, M.; Broggin, M.

CORPORATE SOURCE: Ist. Ricerche Farmacol. Mario Negri, Milan, 20157, Italy

SOURCE: Anti-Cancer Drug Design (1995), 10(8), 641-53

CODEN: ACDDEA; ISSN: 0266-9536

PUBLISHER: Oxford University Press



DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB New alkylating anthracycline derivs. with promising antitumor activity have been synthesized. We selected two of these compds., 4-demethoxy-N,N-bis (2 chloroethyl)-4'-methylsulfonyl-daunorubicin (FCE 27726) and 4-demethoxy-3'-deamino-3'-aziridiny-4'-methylsulfonyl daunorubicin (FCE 28729), comparing their interaction with DNA and that of the non-alkylating deriv. 4-demethoxy-4'-methylsulfonyl-daunorubicin (FCE 27894). The two alkylating derivs. were more cytotoxic than idarubicin and presented low cross-resistance with doxorubicin. Both FCE 27726 and FCE 28729 were found to alkylate guanines at the N7 position in the major groove with roughly the same specificity, but at different concns. FCE 27726 was 10 times more potent than FCE 28729 in alkylating DNA. At higher concns., FCE 27726 was able to alkylate adenines, possibly at the N3 position contained in a sequence 5'-PyAA. FCE 27726, as expected, was able to form DNA inter-strand cross-links either in vitro and in vivo in treated cells. FCE 28729 did not form DNA inter-strand cross-links in vivo. In vitro, at high concns., some DNA inter-strand cross-links were evident. The non-alkylating deriv. FCE 27894 did not produce any alkylation or DNA inter-strand cross-links either in vitro or in vivo.

L4 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 1995:279633 CAPLUS  
DOCUMENT NUMBER: 122:71371  
TITLE: Synthesis and study of structure-activity relationships of new classes of anthracyclines  
AUTHOR(S): Suarato, Antonino; Angelucci, Francesco; Bargiotti, Alberto; Caruso, Michele; Faiardi, Daniela; Capolongo, Laura; Geroni, Cristina; Ripamonti, Marina; Grandi, Maria  
CORPORATE SOURCE: R&D Oncology-Immunology, Pharmacia-Farmitalia Carlo Erba, Milan, 20159, Italy  
SOURCE: ACS Symposium Series (1995), 574(Anthracycline Antibiotics), 142-55  
CODEN: ACSMC8; ISSN: 0097-6156  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Structure-activity studies in the field of anthracyclines have been very fruitful in defining those moieties that are necessary to produce derivs. active on MDR tumor cells. The authors have found that substitutions on the sugar part of anthracyclines are fundamental to confer activity on MDR cells in vitro. In particular, compds. substituted at C-3' of the sugar moiety with 4-morpholino group or selected potential alkylating moieties are able to overcome resistance both in vitro and in vivo.

=> s 13/BAC

9 L3  
1012758 BAC/RL  
L5 7 L3/BAC  
(L3 (L) BAC/RL)

=> dis 15 1-7 ibib abs hitstr

L5 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2001:63809 CAPLUS  
DOCUMENT NUMBER: 134:110448  
TITLE: Synergistic composition comprising daunorubicin derivatives and antimetabolite compounds  
INVENTOR(S): Geroni, Maria Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino  
PATENT ASSIGNEE(S): Pharmacia and Upjohn S.p.A., Italy  
SOURCE: PCT Int. Appl., 12 pp.

CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005382	A1	20010125	WO 2000-EP6545	20000710
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG EP 1200099 A1 20020502 EP 2000-949297 20000710 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: GB 1999-16882 A 19990719  
WO 2000-EP6545 W 20000710

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an antimetabolite compd. in the treatment of tumors, esp. in the treatment or prevention of metastasis or in the treatment of tumors by the inhibition of angiogenesis is described. Thus, at a dose of 15 and 60 mg/kg of gemcitabine alone (i.p. day 1 after tumor injection), PNU 159548 alone (i.v. day 1 after tumor injection, administered 2 after gemcitabine), were assocd., without toxicity, with ILS% values of 50 and 83 and 33 and 67, resp. By combining gemcitabine and PNU 159548 at the same doses and with the same schedule, an increase of activity with ILS% values of 117 and 204 were obsd., indicating a synergistic effect as shown by the combination index (CI) of 1.4 and 1.3, resp.

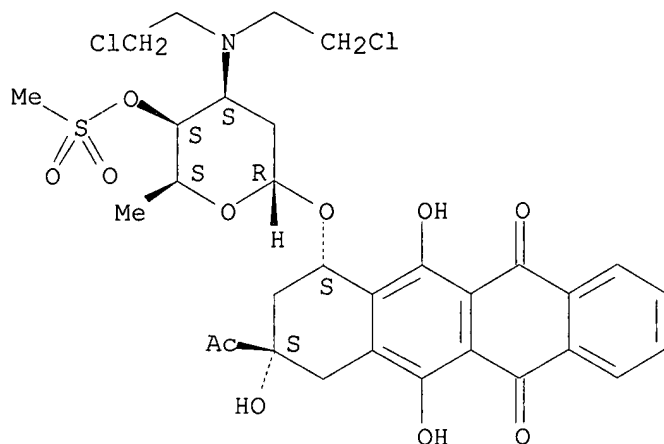
IT 148429-22-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(synergistic compn. comprising daunorubicin derivs. and antimetabolite compds.)

RN 148429-22-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:608575 CAPLUS

DOCUMENT NUMBER: 133:187947

TITLE: Antitumor synergistic combination of daunorubicin derivative and an antimitotic

INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.P.A., Italy

SOURCE: PCT Int. Appl., 13 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050033	A2	20000831	WO 2000-EP746	20000131
WO 2000050033	A3	20001221		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1169035	A2	20020109	EP 2000-904990	20000131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008454	A	20020129	BR 2000-8454	20000131
JP 2002537334	T2	20021105	JP 2000-600644	20000131
PRIORITY APPLN. INFO.: GB 1999-4386 A 19990225				
WO 2000-EP746 W 20000131				

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridiny-4'-methansulfonyldaunorubicin (I) or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an anti-neoplastic anti-mitotic compd. and/or a platinum deriv. in the treatment of tumors, as well as in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis is disclosed. A dose of 8 mg/kg of oxaliplatin alone (day +3) and a dose of 1 mg/kg I alone (days +1,2) were assocd.,

without toxicity, with an increase in the lifespan (ILS) values of 83% for both., when the antileukemic activity was detd. in L1210 murine leukemia. Combining oxaliplatin and I at the same doses with the same schedule an increase in the antitumor activity with ILS values of 125% was obsd., indicating a synergistic effect of the combination.

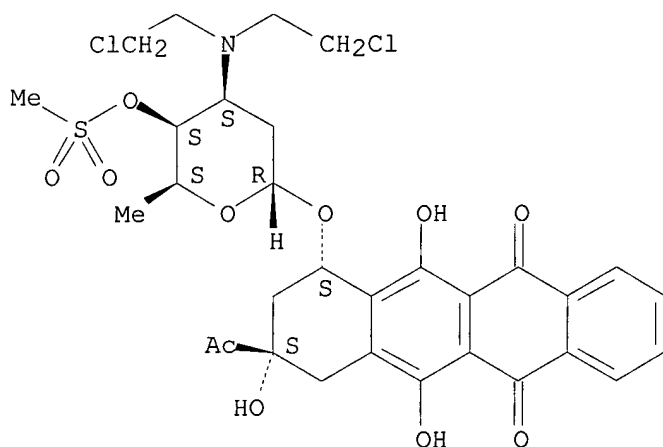
IT 148429-22-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(antitumor synergetic combination of daunorubicin deriv. and antimitotic)

RN 148429-22-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:608574 CAPLUS

DOCUMENT NUMBER: 133:187946

TITLE: Antitumour synergistic combination of daunorubicin derivative and topoisomerase II inhibitor

INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 13 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050032	A1	20000831	WO 2000-EP745	20000131
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,			

CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
 EP 1165069 A1 20020102 EP 2000-903657 20000131  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO  
 BR 2000008453 A 20020129 BR 2000-8453 20000131  
 JP 2002537333 T2 20021105 JP 2000-600643 20000131  
 PRIORITY APPLN. INFO.: GB 1999-4387 A 19990225  
 WO 2000-EP745 W 20000131

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin (I) or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an antineoplastic topoisomerase II inhibitor in the treatment of tumors and the use of the combination in the treatment or prevention of metastasis or in the treatment of tumors by inhibition of angiogenesis are disclosed. A dose of 13 mg/kg of doxorubicin alone (day +3) and a dose of 1.5 mg/kg I alone (days +1,2) were assocd., without toxicity, with an increase in the lifespan (ILS) values of 50 and 67%, resp. Combining doxorubicin at the same doses with the same schedule an increase in the antitumor activity with ILS values of 150% was obsd., indicating a synergistic effect of the combination.

IT 148429-22-5

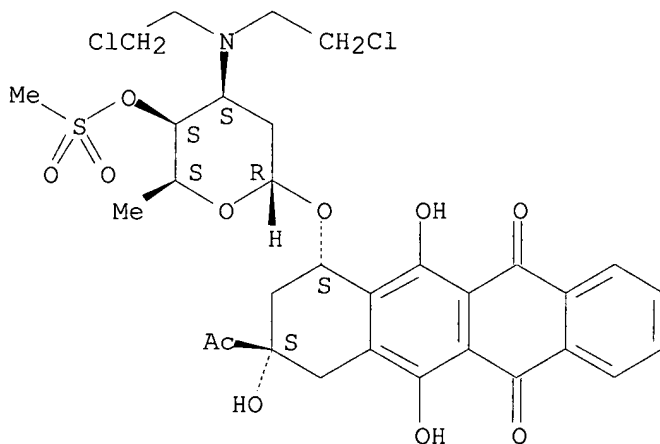
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antitumor synergistic combination of daunorubicin deriv. and topoisomerase II inhibitor)

RN 148429-22-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:626051 CAPLUS

DOCUMENT NUMBER: 131:252552

TITLE: Antitumor composition containing a synergistic combination of an anthracycline derivative with a camptothecin derivative

INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 14 pp.

CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9948503	A1	19990930	WO 1999-EP1897	19990319
W: AU, BG, BR, CA, CN, CZ, HU, ID, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2324610	AA	19990930	CA 1999-2324610	19990319
AU 9933314	A1	19991018	AU 1999-33314	19990319
BR 9908391	A	20001031	BR 1999-8391	19990319
EP 1067941	A1	20010117	EP 1999-914528	19990319
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002507571	T2	20020312	JP 2000-537551	19990319
ZA 9902255	A	19991005	ZA 1999-2255	19990323
NO 2000004703	A	20000920	NO 2000-4703	20000920
US 6403563	B1	20020611	US 2000-646096	20000920
PRIORITY APPLN. INFO.:				
			GB 1998-6324	A 19980324
			WO 1999-EP1897	W 19990319

AB There are provided the combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and an antineoplastic topoisomerase I inhibitor in the treatment of tumors and the use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin in the treatment of brain tumors.

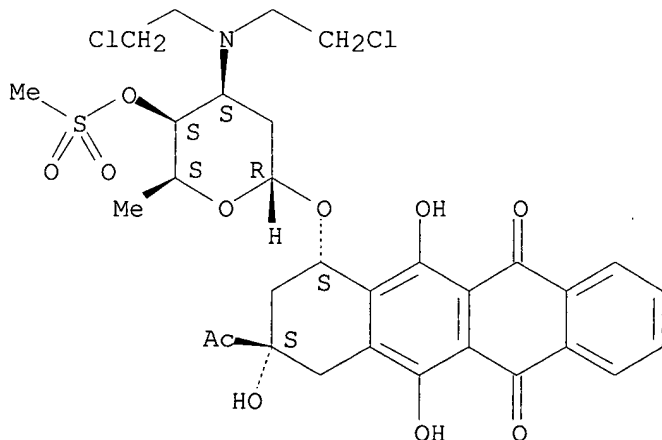
IT 148429-22-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(anthracycline deriv.-camptothecin compd. antitumor synergistic combination and compn.)

RN 148429-22-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:279633 CAPLUS

DOCUMENT NUMBER: 122:71371

TITLE: Synthesis and study of structure-activity relationships of new classes of anthracyclines

AUTHOR(S): Suarato, Antonino; Angelucci, Francesco; Bargiotti, Alberto; Caruso, Michele; Faiardi, Daniela; Capolongo, Laura; Geroni, Cristina; Ripamonti, Marina; Grandi, Maria

CORPORATE SOURCE: R&D Oncology-Immunology, Pharmacia-Farmitalia Carlo Erba, Milan, 20159, Italy

SOURCE: ACS Symposium Series (1995), 574(Anthracycline Antibiotics), 142-55

CODEN: ACSMC8; ISSN: 0097-6156

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Structure-activity studies in the field of anthracyclines have been very fruitful in defining those moieties that are necessary to produce derivs. active on MDR tumor cells. The authors have found that substitutions on the sugar part of anthracyclines are fundamental to confer activity on MDR cells in vitro. In particular, compds. substituted at C-3' of the sugar moiety with 4-morpholino group or selected potential alkylating moieties are able to overcome resistance both in vitro and in vivo.

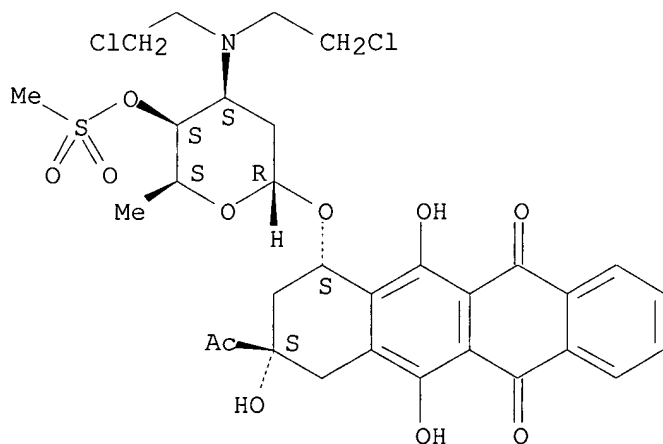
IT 148429-22-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(structure-activity relationships of new classes of anthracyclines as neoplasm inhibitors)

RN 148429-22-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:265031 CAPLUS

DOCUMENT NUMBER: 122:95937

TITLE: Growth-inhibitory properties of novel anthracyclines

in human leukemic cell lines expressing either Pgp-MDR or at-MDR

AUTHOR(S): Mariani, Mariangela; Capolongo, Laura; Suarato, Antonino; Bargiotti, Alberto; Mongelli, Nicola; Grandi, Maria; Beck, William T.

CORPORATE SOURCE: Research Center, Pharmacia-Farmitalia Carlo Erba, Milan, Italy

SOURCE: Investigational New Drugs (1994), 12(2), 93-7  
CODEN: INNDDK; ISSN: 0167-6997

PUBLISHER: Kluwer

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The objective of the expts. reported in this paper was the identification of promising anthracycline analogs on the basis of lack of cross-resistance against tumor cells presenting either P-glycoprotein multidrug resistance (Pgp-MDR) or the altered topoisomerase multidrug resistant (at-MDR) phenotype. Differently modified anthracycline analogs known to be active against MDR cells were assayed in vitro against CEM human leukemic cells, and the sublines CEM/VLB100 and CEM/VM-1 exhibiting resp. the Pgp-MDR and the at-MDR phenotype. Two classes of mols., in which the -NH<sub>2</sub> group in C-3' position is substituted with a morpholino, methoxymorpholino (morpholinyl-anthracycline), or an alkylating moiety, present equiv. efficacy in the drug-sensitive and the two drug-resistant sublines. These results indicate that such mols. may exert their cytotoxic effect through a mode of action different from that of "classical" anthracyclines and is not mediated through topoisomerase II inhibition. Both mols. represent novel concepts in the field of new anthracyclines derivs.

IT 148429-22-5

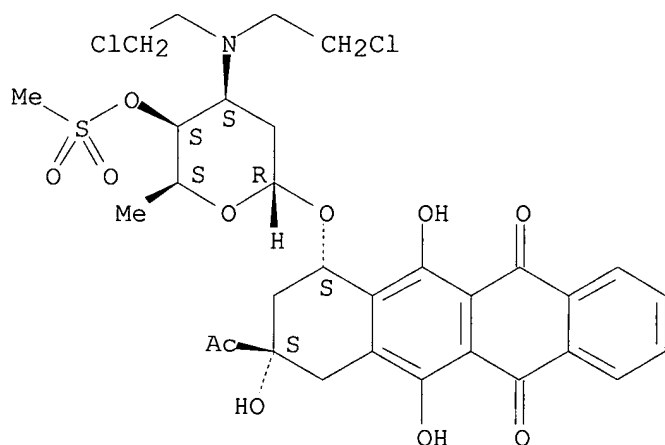
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(growth-inhibitory properties of anthracyclines in human leukemic cell lines expressing either P-glycoprotein or altered topoisomerase multidrug resistant phenotype)

RN 148429-22-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

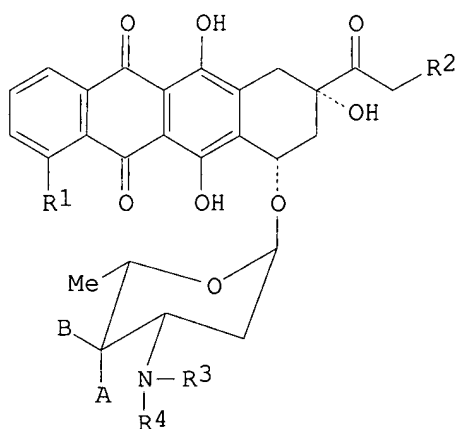
Absolute stereochemistry.





DOCUMENT NUMBER: 119:96068  
 TITLE: Preparation of alkylamino anthracycline glycosides as antitumors.  
 INVENTOR(S): Bargiotti, Alberto; Caruso, Michele; Faiardi, Daniella; Suarato, Antonino; Mongelli, Nicola  
 PATENT ASSIGNEE(S): Farmitalia Carlo Erba S.r.l., Italy  
 SOURCE: Eur. Pat. Appl., 13 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 521458	A1	19930107	EP 1992-111054	19920630
EP 521458	B1	19960221		
R: AT, BE, DE, DK, FR, GB, GR, IT, NL, PT				
US 5496808	A	19960305	US 1992-904650	19920626
AT 134376	E	19960315	AT 1992-111054	19920630
CA 2112818	AA	19930121	CA 1992-2112818	19920703
WO 9301201	A1	19930121	WO 1992-EP1504	19920703
W: AU, CA, CS, FI, HU, JP, KR, NO, RU				
AU 9222294	A1	19930211	AU 1992-22294	19920703
AU 661012	B2	19950713		
ZA 9204971	A	19930331	ZA 1992-4971	19920703
HU 70480	A2	19951030	HU 1994-22	19920703
HU 218913	B	20001228		
IL 102409	A1	19951208	IL 1992-102409	19920703
RU 2118328	C1	19980827	RU 1994-21658	19920703
JP 3153552	B2	20010409	JP 1993-501958	19920703
CN 1069981	A	19930317	CN 1992-108867	19920704
CN 1031878	B	19960529		
NO 9400026	A	19940216	NO 1994-26	19940104
PRIORITY APPLN. INFO.:			GB 1991-14549	A 19910705
			WO 1992-EP1504	A 19920703
OTHER SOURCE(S):		MARPAT 119:96068		
GI				



I

AB The title compds. [I; R1 = H, MeO; R2 = H, OH; A, B = H, OH, OSO2R5; R5 = (un)substituted C1-4 alkyl, aryl; R3 = H, (CH2)n-X; R4 = (CH2)n-X; n = 2, 3; X = OH, halo; A = B = H, or one of them = H and the other = OH or OSO2R5; with provisos] and their pharmaceutically acceptable salts are prepd. Daunorubicin was reacted with 3-bromo-1-propanol in DMF at room

temp. for 5 days to give 54% I [R1 = MeO, R2 = R3 = H, A = OH, B = H, R4 = (CH2)3OH]. 4-Demethoxy-4'-O-methylsulfonyl-N,N-bis(2-chloroethyl)daunorubicin (also prepd.) had an IC50 of 14.0 ng/mL against human colon adenocarcinoma cells LoVo in vitro vs. 4975 ng/mL for doxorubicin.

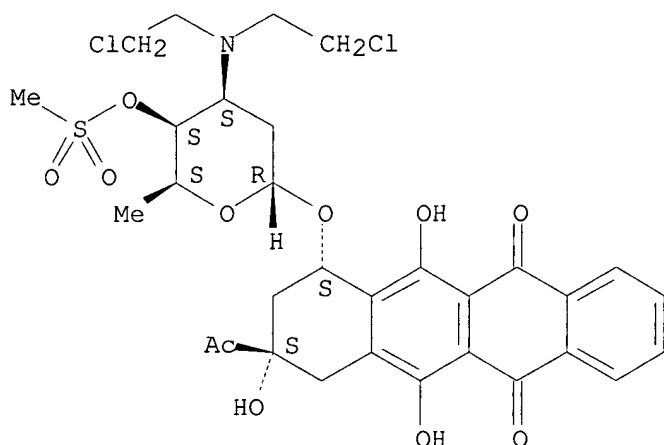
IT 148429-22-5P 148429-24-7P 148496-75-7P  
148496-77-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(prepn. of, as antitumor)

RN 148429-22-5 CAPLUS

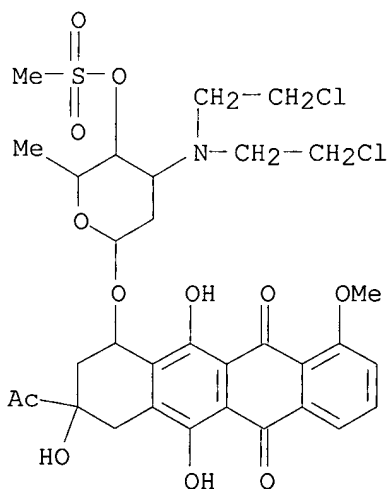
CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



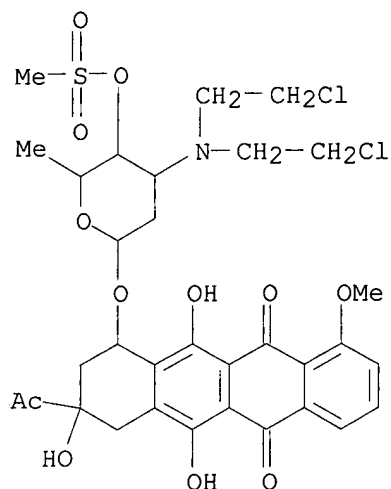
RN 148429-24-7 CAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)- (9CI) (CA INDEX NAME)



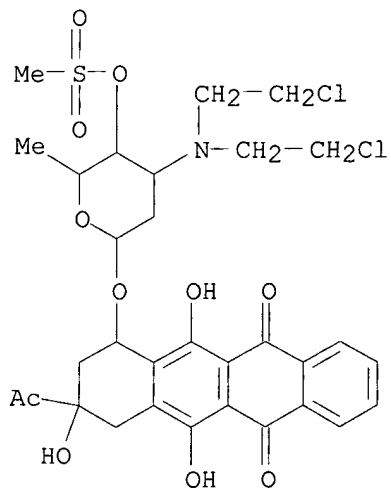
RN 148496-75-7 CAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[bis(2-chloroethyl) amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-arabino-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)- (9CI) (CA INDEX NAME)



RN 148496-77-9 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl) amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-arabino-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S-cis)- (9CI) (CA INDEX NAME)



=> s l3/THU and gemcitabine

9 L3

477649 THU/RL

7 L3/THU

(L3 (L) THU/RL)

1244 GEMCITABINE

L6

1 L3/THU AND GEMCITABINE

=> dis l6 ibib abs hitstr

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2001:63809 CAPLUS  
 DOCUMENT NUMBER: 134:110448  
 TITLE: Synergistic composition comprising daunorubicin derivatives and antimetabolite compounds  
 INVENTOR(S): Geroni, Maria Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino  
 PATENT ASSIGNEE(S): Pharmacia and Upjohn S.p.A., Italy  
 SOURCE: PCT Int. Appl., 12 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005382	A1	20010125	WO 2000-EP6545	20000710
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1200099	A1	20020502	EP 2000-949297	20000710
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: GB 1999-16882 A 19990719  
 WO 2000-EP6545 W 20000710

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an antimetabolite compd. in the treatment of tumors, esp. in the treatment or prevention of metastasis or in the treatment of tumors by the inhibition of angiogenesis is described. Thus, at a dose of 15 and 60 mg/kg of **gemcitabine** alone (i.p. day 1 after tumor injection), PNU 159548 alone (i.v. day 1 after tumor injection, administered 2 after **gemcitabine**), were assocd., without toxicity, with ILS% values of 50 and 83 and 33 and 67, resp. By combining **gemcitabine** and PNU 159548 at the same doses and with the same schedule, an increase of activity with ILS% values of 117 and 204 were obsd., indicating a synergistic effect as shown by the combination index (CI) of 1.4 and 1.3, resp.

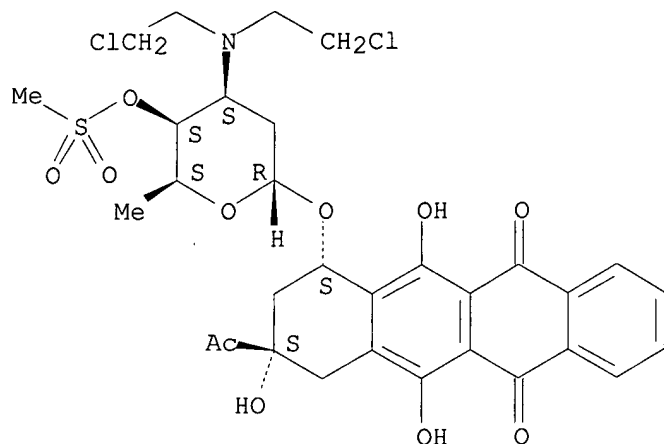
IT **148429-22-5**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)  
 (synergistic compn. comprising daunorubicin derivs. and antimetabolite compds.)

RN 148429-22-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s 13/THU and 5-fluorouracil

9 L3  
477649 THU/RL  
7 L3/THU  
(L3 (L) THU/RL)  
5298256 5  
13659 FLUOROURACIL  
268 FLUOROURACILS  
13672 FLUOROURACIL  
(FLUOROURACIL OR FLUOROURACILS)  
12257 5-FLUOROURACIL  
(5(W) FLUOROURACIL)

L7 0 L3/THU AND 5-FLUOROURACIL

=> s 13/THU and fluoropyrimidine

9 L3  
477649 THU/RL  
7 L3/THU  
(L3 (L) THU/RL)  
826 FLUOROPYRIMIDINE  
470 FLUOROPYRIMIDINES  
1017 FLUOROPYRIMIDINE  
(FLUOROPYRIMIDINE OR FLUOROPYRIMIDINES)

L8 1 L3/THU AND FLUOROPYRIMIDINE

=> dis 18 ibib abs hitstr

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:63809 CAPLUS

DOCUMENT NUMBER: 134:110448

TITLE: Synergistic composition comprising daunorubicin derivatives and antimetabolite compounds

INVENTOR(S): Geroni, Maria Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia and Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 12 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005382	A1	20010125	WO 2000-EP6545	20000710
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1200099	A1	20020502	EP 2000-949297	20000710
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: GB 1999-16882 A 19990719  
WO 2000-EP6545 W 20000710

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an antimetabolite compd. in the treatment of tumors, esp. in the treatment or prevention of metastasis or in the treatment of tumors by the inhibition of angiogenesis is described. Thus, at a dose of 15 and 60 mg/kg of gemcitabine alone (i.p. day 1 after tumor injection), PNU 159548 alone (i.v. day 1 after tumor injection, administered 2 after gemcitabine), were assocd., without toxicity, with ILS% values of 50 and 83 and 33 and 67, resp. By combining gemcitabine and PNU 159548 at the same doses and with the same schedule, an increase of activity with ILS% values of 117 and 204 were obsd., indicating a synergistic effect as shown by the combination index (CI) of 1.4 and 1.3, resp.

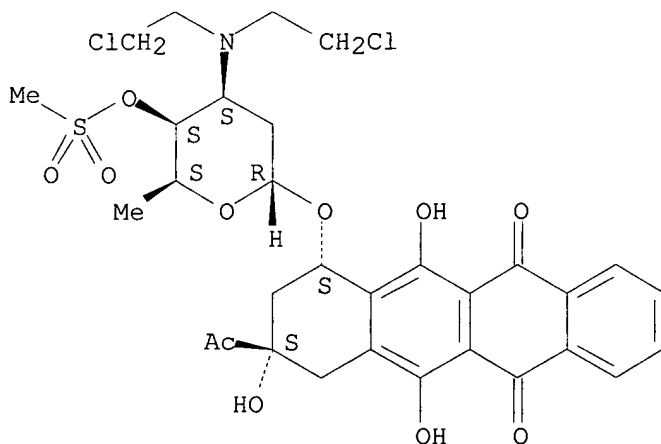
IT 148429-22-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(synergistic compn. comprising daunorubicin derivs. and antimetabolite compds.)

RN 148429-22-5 CAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



significantly higher activity of TP in **tumor** compared with healthy tissue. The high single-agent activity of capecitabine in breast and colorectal **cancer** suggests that capecitabine may have a role in the treatment of other **tumor** types that are sensitive to 5-FU, such as pancreatic **cancer**. **Tumor** types known to have a high level of TP activity, such as renal **cancer**, are esp. attractive targets for capecitabine therapy. Capecitabine has potential as monotherapy in these **tumor** types, or as a combination partner for other cytotoxic agents with different mechanisms of action and little overlap of key toxicities. In particular, some cytotoxic drugs, such as the taxanes and cyclophosphamide, are known to upregulate TP activity in **tumor** tissue, offering the potential for **synergistic** action. The combination of capecitabine and docetaxel has demonstrated significant activity in women with **anthracycline**-pretreated breast **cancer**, and is the only cytotoxic combination to significantly increase survival compared with std. therapy in this setting. In addn., capecitabine as monotherapy or in combination with other cytotoxic agents has shown encouraging activity in pancreatic, ovarian, and renal cell **cancers**. This article discusses recent data from clin. trials investigating capecitabine in a range of **tumor** types, highlighting the potential future role of capecitabine as an alternative to traditional i.v. chemotherapy.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:311905 HCAPLUS

DOCUMENT NUMBER: 135:204779

TITLE: The platinum agents: a role in breast **cancer** treatment?

AUTHOR(S): Crown, John P.

CORPORATE SOURCE: Department of Medical Oncology, St Vincent's University Hospital, Dublin, Ire.

SOURCE: Seminars in Oncology (2001), 28(1, Suppl. 3), 28-37  
CODEN: SOLGAV; ISSN: 0093-7754

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 65 refs. **Metastatic** breast **cancer** is a partially chemotherapy-sensitive **neoplasm**. Most chemotherapy groups have activity in this disease, and the most active single drugs are the taxanes, esp. docetaxel (Taxotere; Aventis Pharmaceuticals, Inc, Parsippany, NJ), and the **anthracyclines**. The alkylating agents, **antimetabolites**, and vinca alkaloids are also widely used. The platinum coordination complexes, which are widely used in oncol., are also active in **metastatic** breast **cancer**, but the availability of other drugs that are less toxic and easier to administer has resulted in their having a strictly limited use in this setting. Cisplatin appears to be somewhat more active than carboplatin, but direct comparative studies are lacking. The identification of the prominent activity of the taxanes has led to the investigation of wholly novel non-**anthracycline**-contg. combination regimens, and platinum/taxane doublets appear to be particularly active. More recently, reports that trastuzumab (Herceptin, Genentech, South San Francisco, CA), a novel

monoclonal antibody directed against the protein product of the HER2/neu oncogene, has a powerful **synergistic** interaction with docetaxel and with platinum agents have prompted evaluation of the triplet docetaxel/platinum/trastuzumab in the therapy of **metastatic breast cancer**.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:790283 HCAPLUS

DOCUMENT NUMBER: 133:344606

TITLE: Combined pharmaceuticals comprising anthracycline derivatives

INVENTOR(S): Geroni, Maria Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 23 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 2000066093	A2	20001109	WO 2000-EP2923	20000404	check
WO 2000066093	A3	20010125			
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
EP 1173187	A2	20020123	EP 2000-925158	20000404	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
PRIORITY APPLN. INFO.:			GB 1999-9925	A 19990429	
			WO 2000-EP2923	W 20000404	

AB The present invention relates to combined pharmaceuticals comprising a morpholinylanthracycline administered in combination **anticancer** agents chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum deriv., which are useful in **anticancer** therapy, particularly in the treatment of a primary or **metastatic** liver **cancer**. At doses 5.9 and 7,7 mg/kg cis-platin administered alone and 0.05 mg/kg PNU-152243 (morpholinylanthracycline) administered alone, the increase in lifespan values was 33, 33 and 50%. Sequential administration of these drugs showed a therapeutic advantage of the combination in comparison with each drug administered alone.

IT 51-21-8, 5-Fluorouracil 147-94-4, Cytarabine 10212-20-1 95058-81-4, Gemcitabine



154361-50-9, Capecitabine

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(combined pharmaceuticals comprising **anthracycline** derivs.)

L21 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:626406 HCAPLUS

DOCUMENT NUMBER: 134:320570

TITLE: Induction of apoptosis using  
2',2'-difluorodeoxycytidine (**gemcitabine**) in  
combination with **antimetabolites** or  
**anthracyclines** on malignant lymphatic and  
myeloid cells. Antagonism or synergism depends on  
incubation schedule and origin of **neoplastic**  
cells

AUTHOR(S): Chow, K. U.; Ries, J.; Weidmann, E.; Pourebrahim, F.;  
Napieralski, S.; Stieler, M.; Boehrer, S.; Rummel, M.  
J.; Stein, J.; Hoelzer, D.; Mitrou, P. S.

CORPORATE SOURCE: Hematology/Oncology, Department of Internal Medicine  
III, Johann Wolfgang Goethe-University Hospital,  
Frankfurt, D-60590, Germany

SOURCE: Annals of Hematology (2000), 79(9), 485-492  
CODEN: ANHEE8; ISSN: 0939-5555

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Induction of apoptosis in vitro using gemcitabine (dFdC) in combination with cladribine (2-CdA) and other cytotoxic drugs on malignant mononuclear cells (MNCs) of patients with acute myeloid **leukemia** (AML,n=20) and chronic lymphocytic **leukemia** (CLL,n=20) in myeloid (HL60, HEL) and lymphatic cell lines (HUT78, JURKAT) was investigated using different incubation conditions (simultaneous and consecutive). Furthermore, the influence of dFdC on the level of intracellular metabolites of 2-CdA was studied using high-performance liq. chromatog. (HPLC). Apoptosis was evaluated using flow cytometry with 7-aminoactinomycin D. In MNCs of patients with CLL, dFdC+2-CdA showed an antagonistic effect when applied simultaneously. This antagonism was reduced by consecutive application. The combination of dFdC with doxorubicin was **synergistic**, independent of incubation schedule. In blasts from newly diagnosed patients with de novo AML, all drug combinations (dFdC+2-CdA, doxorubicin, or cytosine arabinoside) were antagonistic by simultaneous incubation. Reduced antagonism or even synergism was shown by consecutive incubation. The simultaneous combination of dFdC with 2-CdA in all tested cell lines resulted in a competitive inhibition on the rate of apoptosis. By changing the incubation period to a consecutive schedule, the antagonism was diminished or synergism of apoptosis was measured. Using similar incubation conditions, these expts. were supported by HPLC measurement of intracellular metabolites of 2-CdA influenced by dFdC application. In conclusion, the authors demonstrated that the efficacy of dFdC in vitro in combination with other cytotoxic drugs depends on the incubation condition and on the origin of **neoplastic** cells (lymphatic vs myeloid). The data suggest that simultaneous combination therapy with purine and pyrimidine analogs may not improve the clin. efficacy of 1 or the other drug administered alone.

IT 95058-81-4, Gemcitabine

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
(apoptosis induction by **gemcitabine** in combination with **antimetabolites** or **anthracyclines** on malignant lymphatic and myeloid cells)

IT 147-94-4, Cytosine arabinoside

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(apoptosis induction by **gemcitabine** in combination with **antimetabolites** or **anthracyclines** on malignant lymphatic and myeloid cells)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:466885 HCAPLUS

DOCUMENT NUMBER: 133:202652

TITLE: **Anticancer** derivative of butyric acid  
(pivalyloxymethyl butyrate) specifically potentiates the cytotoxicity of doxorubicin and daunorubicin through the suppression of microsomal glycosidic activity

AUTHOR(S): Niitsu, Nozomi; Kasukabe, Takashi; Yokoyama, Akihiro; Okabe-Kado, Junko; Yamamoto-Yamaguchi, Yuri; Umeda, Masanori; Honma, Yoshio

CORPORATE SOURCE: Saitama Cancer Center Research Institute, Saitama, Japan

SOURCE: Molecular Pharmacology (2000), 58(1), 27-36  
CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Pivalyloxymethyl butyrate (AN9) is an **anticancer** deriv. of butyric acid. In this study, doxorubicin (DXR) and AN9 **synergistically** inhibited the growth of lymphoma and lung **carcinoma** cells, whereas there was no synergy between AN9 and **antimetabolites**. AN9 did not affect the intracellular uptake of DXR. Among **anthracyclines** and their derivs., the **synergistic** effect was prominent in compds. with a daunosamine moiety, suggesting that AN9 may affect the catabolism of these compds. The degrdn. of DXR in the ext. from AN9-treated cells was much less than that in ext. from untreated cells. AN9 did not directly inhibit the enzyme activity but rather suppressed expression of the enzyme. With respect to the expression of drug resistance-related genes, there was no significant difference between untreated and AN9-treated cells. However, AN9 significantly down-regulated the levels NADPH-cytochrome P 450 reductase and DT-diaphorase mRNA in the presence of DXR but not the level of xanthine oxidase mRNA. The enhancement of the sensitivity to **anthracyclines** was closely assocd. with the suppression of the mRNA expression.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:269587 HCAPLUS

DOCUMENT NUMBER: 131:67755

TITLE: Inhibitory effects of combinations of HER-2/neu

antibody and chemotherapeutic agents used for treatment of human breast **cancers**

AUTHOR(S): Pegram, Mark; Hsu, Sheree; Lewis, Gail; Pietras, Richard; Beryt, Malgorzata; Sliwkowski, Mark; Coombs, Daniel; Baly, Deborah; Kabbinavar, Fairouz; Slamon, Dennis

CORPORATE SOURCE: Division of Hematology-Oncology, UCLA School of Medicine, Los Angeles, CA, 90095, USA

SOURCE: Oncogene (1999), 18(13), 2241-2251

CODEN: ONCNES; ISSN: 0950-9232

PUBLISHER: Stockton Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Previous studies have demonstrated a **synergistic** interaction between rhuMab HER2 and the cytotoxic drug cisplatin in human breast and ovarian **cancer** cells. To define the nature of the interaction between rhuMab HER2 and other classes of cytotoxic drugs, the authors applied multiple drug effect/combination index (CI) isobologram anal. to a variety of chemotherapeutic drug/rhuMab HER2 combinations in vitro. **Synergistic** interactions at clin. relevant drug concns. were obsd. for rhuMab HER2 in combination with cisplatin (CI = 0.48, P = 0.003), thiotepa (CI = 0.67, P = 0.0008), and etoposide (CI = 0.54, P = 0.0003). Additive cytotoxic effects were obsd. with rhuMab HER2 plus doxorubicin (CI = 1.16, P = 0.13), paclitaxel (CI = 0.91, P = 0.21), methotrexate (CI = 1.15, P = 0.28), and vinblastine (CI = 1.09, P = 0.26). One drug, 5-**fluorouracil**, was found to be antagonistic with rhuMab HER2 in vitro (CI = 2.87, P = 0.0001). In vivo drug/rhuMab HER2 studies were conducted with HER-2/neu-transfected, MCF7 human breast **cancer** xenografts in athymic mice. Combinations of rhuMab HER2 plus cyclophosphamide, doxorubicin, paclitaxel, methotrexate, etoposide, and vinblastine in vivo resulted in a significant redn. in xenograft vol. compared to chemotherapy alone (P<0.05). Xenografts treated with rhuMab HER2 plus 5-**fluorouracil** were not significantly different from 5-**fluorouracil** alone controls consistent with the subadditive effects obsd. with this combination in vitro. The **synergistic** interaction of rhuMab HER2 with alkylating agents, platinum analogs and topoisomerase II inhibitors, as well as the additive interaction with taxanes, **anthracyclines** and some **antimetabolites** in HER-2/neu-overexpressing breast **cancer** cells demonstrates that these are rational combinations to test in human clin. trails.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:534304 HCAPLUS

DOCUMENT NUMBER: 129:225398

TITLE: Enhancement of chemotherapeutic drug toxicity to human

AUTHOR(S): tumor cells in vitro by a subset of  
non-steroidal anti-inflammatory drugs (NSAIDs)  
Duffy, C. P.; Elliott, C. J.; O'Connor, R. A.; Heenan,  
M. M.; Coyle, S.; Cleary, I. M.; Kavanagh, K.;  
Verhaegen, S.; O'Loughlin, C. M.; NicAmhlaoibh, R.;  
Clynes, M.  
CORPORATE SOURCE: National Cell and Tissue Culture Centre, Dublin City  
University, Dublin, Ire.  
SOURCE: European Journal of Cancer (1998), 34(8), 1250-1259 ←  
CODEN: EJCAEL; ISSN: 0959-8049  
PUBLISHER: Elsevier Science Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The effect on cytotoxicity of combining a range of clin. important  
non-steroidal anti-inflammatory drugs (NSAIDs) with a variety of  
chemotherapeutic drugs was examd. in the human lung **cancer** cell  
lines DLKP, A549, COR L23P, and COR L23R and in a human **leukemia**  
line HL60/ADR. A specific group of NSAIDs (indomethacin, sulindac,  
tolmetin, acemetacin, zomepirac, and mefenamic acid) all at non-toxic  
levels, increased the cytotoxicity of the **anthracyclines**  
(doxorubicin, daunorubicin, and epirubicin), as well as teniposide, VP-16,  
and vincristine, but not the other vinca alkaloids vinblastine and  
vinorelbine. A substantial no. of **anticancer** drugs, including  
methotrexate, 5-**fluorouracil**, cytarabine, hydroxyurea,  
chlorambucil, cyclophosphamide, cisplatin, carboplatin, mitoxantrone,  
actinomycin D, bleomycin, paclitaxel, and camptothecin, were also tested,  
but displayed no synergy in combination with the NSAIDs. The  
**synergistic** effect was concn. dependent. The effect appears to be  
independent of the cyclo-oxygenase inhibitory ability of the NSAIDs, as  
(i) the **synergistic** combination was not reversed by the addn. of  
prostaglandins D2 or E2; (ii) sulindac sulfone, a metabolite of sulindac  
that does not inhibit the cyclooxygenase enzyme, was pos. in the  
combination assay; and (iii) many NSAIDs known to be cyclo-oxygenase  
inhibitors, e.g. meclofenamic acid, diclofenac, naproxen, fenoprofen,  
phenylbutazone, flufenamic acid, flurbiprofen, ibuprofen, and ketoprofen,  
were inactive in the combination assay. The enhancement of cytotoxicity  
was obsd. in drug sensitive **tumor** cell lines, but did not occur  
in P-170-overexpressing multidrug resistant cell lines. In the HL60/ADR  
and COR L23R cell lines, in which multidrug resistance is due to  
overexpression of the multidrug resistance-assocd. protein MRP, an  
increase in cytotoxicity was obsd. in the presence of the active NSAIDs.  
Subsequent Western blot of the drug sensitive parental cell lines, DLKP  
and A549, revealed that they also expressed MRP and reverse-transcription-  
PCR studies demonstrated that mRNA for MRP was present in both cell lines.  
It was found that the pos. NSAIDs were among the more potent inhibitors of  
[3H]-LTC4 transport into inside-out plasma membrane vesicles prepd. from  
MRP-expressing cells, of doxorubicin efflux from preloaded cells and of  
glutathione-S-transferase activity. The NSAIDs did not enhance cellular  
sensitivity to radiation. The combination of specific NSAIDs with  
**anticancer** drugs may have potential clin. applications, esp. in  
the circumvention of MRP-mediated multidrug resistance.

L21 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 1998:417113 HCAPLUS

DOCUMENT NUMBER: 129:156578  
 TITLE: Combination of cisplatin-procaine complex DPR with **anticancer** drugs increases cytotoxicity against ovarian **cancer** cell lines  
 AUTHOR(S): Viale, Maurizio; Pastrone, Ilaria; Pellecchia, Caterina; Vannozzi, Maria O.; Cafaggi, Sergio; Esposito, Mauro  
 CORPORATE SOURCE: Inst. Nazionale per la Ricerca sul Cancro, Servizio di Farmacologia Tossicologica, Genoa, 16132, Italy  
 SOURCE: Anti-Cancer Drugs (1998), 9(5), 457-463  
 CODEN: ANTDEV; ISSN: 0959-4973  
 PUBLISHER: Lippincott-Raven Publishers  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB DPR, cis-diamminechloro-[2-(diethylamino)ethyl 4-amino-benzoate, N4]-chlorideplatinum(II) monohydrochloride monohydrate, is a newly developed water-sol. platinum compd. which possesses minimal cross-resistance to cisplatin and shows relatively less side effects. To establish whether the combination of DPR with other conventional **anticancer** drugs would be of any benefit, the authors assessed in vitro the cytotoxic effects of combinations of DPR with the **antimetabolites** 5-fluorouracil (5-FU) and methotrexate (MTX), the alkylating agents mitomycin C (MMC) and cisplatin, the antimicrotubule agent taxol (TAX), and the intercalating agent of the **anthracycline** group doxorubicin (DOX) on murine M5076 ovarian **reticulosarcoma** and human A2780 ovarian **carcinoma** cells. These agents were selected because of their common use in the clinic and because they represent four distinct categories of **antineoplastic** mechanisms. Cells were incubated for 72 h in the presence of single or combined drugs, and the cytotoxic effect was detd. by the MTT assay. The anal. of combination treatment was made by the isobole method. In human A2780 cells, an overall synergy was found for DPR combined with 5-FU, DOX and cisplatin. **Synergistic** effects were also obsd. for most combinations with MTX or MMC. A DPR concn.-dependent additivity and antagonism was seen at the highest MTX concn. (1 .mu.M), while additive effects were obsd. for the combined treatments of DPR and low concns. of MMC (0.008 and 0.0016 .mu.M). Additive effects were also obsd. for the assocn. of DPR and TAX over most combinations tested. In murine M5076 cells, synergism was the prevailing result obsd. when DPR was combined with 5-FU, DOX, MMC or cisplatin. When administered together with MTX the authors obsd. additively over most combinations tested. These findings suggest that DPR, when simultaneously administered with std. **anticancer** agents, may be advantageous for cytotoxicity.

L21 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:235568 HCAPLUS  
 DOCUMENT NUMBER: 120:235568  
 TITLE: Studies on chemotherapy for malignant lymphoma. 2. Evaluation of **anticancer** drug combination on hematologic malignant cell lines using median effect analysis  
 AUTHOR(S): Ueno, Kunio  
 CORPORATE SOURCE: Med. Sch., Okayama Univ., Okayama, 700, Japan  
 SOURCE: Okayama Igakkai Zasshi (1993), 105(11/12), 1019-30

CODEN: OIZAAV; ISSN: 0030-1558

DOCUMENT TYPE: Journal  
LANGUAGE: Japanese

AB To establish an effective combination chemotherapy for hematol. malignancies, the combined effects of four **anthracycline**-anthraquinones [adriamycin (ADM), aclarubicin (ACR), THP-adriamycin (THP-ADM), and mitoxantrone (MXT)] and five other drugs [4-hydroperoxycyclophosphamide (4HO2-CTX), cytarabine (Ara-C), vincristine (VCR), etoposide (ETP), and cisplatin (CDDP)] were assessed in vitro. Median effect anal. presented by Chou and Talalay was used to assess the combined effects of these drugs on two cell lines (HL-60 and Raji). The ratio of maximal tolerable dose (MTD) to the dose that produced 50% growth inhibition (Dm) was calcd. to est. the clin. activity of each drug. Data of MTD/Dm indicated that THP-ADM and MXT might be clin. superior to ADM and ACR. The results of median effect anal. shown by a combination index were as follows. As to HL-60 cells that were derived from acute promyelocytic **leukemia** cells, **synergistic** effects were seen in the combination of ACR and Ara-C, THP-ADM and CDDP, MXT and 4HO2-CTX, MXT and Ara-C, MXT and VCR, and MXT and ETP, indicating that MXT showed efficient **synergistic** effects when combined with other drugs. As to Raji cells that were derived from Burkitt's lymphoma cells, **synergistic** effects were obsd. in the combinations of ADM and ETP, ADM and CDDP, ACR and VCR, THP-ADM and VCR, THP-ADM and ETP, THP-ADM and CDDP, and MXT and VCR, indicating that THP-ADM showed efficient **synergistic** effects when combined with other drugs.

IT 147-94-4, Cytosine arabinoside  
RL: BIOL (Biological study)  
(lymphoma and **leukemia** response to combination of **anthracyclines** with)

L21 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:153106 HCAPLUS

DOCUMENT NUMBER: 120:153106

TITLE: An Adriamycin-resistant human small-cell lung

**cancer** cell line (SBC-3/ADM100) shows collateral sensitivity to antifolates

AUTHOR(S): Kiura, K.; Ohnoshi, T.; Ueoka, H.; Tabata, M.; Segawa, Y.; Shibayama, T.; Chikamori, T.; Takigawa, N.; Kimura, I.

CORPORATE SOURCE: Med. Sch., Okayama Univ., Okayama, 700, Japan

SOURCE: Int. Congr. Ser. - Excerpta Med. (1993), 1026 (Mechanism and New Approach on Drug Resistance of Cancer Cells), 111-14

CODEN: EXMDA4; ISSN: 0531-5131

DOCUMENT TYPE: Journal

LANGUAGE: English

AB SBC-3/ADM100 was completely cross-resistant to vinca alkaloids (vincristine, vindesine, vinblastine and navelbin), teniposide and epirubicin (a photoisomer of Adriamycin); moderately cross-resistant to a wide variety of **anticancer** agents (**anthracyclines**, anthraquinone, podophyllotoxins, mitomycin-C, bleomycin, peplomycin and topoisomerase I inhibitors), but noncross-resistant to platinum compds. (cisplatin, carboplatin, 254-S), alkylating agents (4-HC and 4-HI) and 5-**fluorouracil**. Collateral sensitivity to antifolates (except for

trimetrexate) was obsd. Relative resistance was 0.52 for TNP-351, 0.70 for methotrexate and 0.87 for edatrexate. This study suggests that a combination of Adriamycin and antifolates might have **synergistic** effects, and antifolates, esp. TNP-351 and edatrexate, might eradicate the residual resistant cells after treatment with Adriamycin.

L21 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:600790 HCAPLUS  
DOCUMENT NUMBER: 119:200790  
TITLE: Apoptosis (programmed cell death) and the evaluation of chemosensitivity in chronic lymphocytic **leukemia** and lymphoma  
AUTHOR(S): Frankfurt, Oskar S.; Byrnes, John J.; Seckinger, Daniel; Sugarbaker, Everett V.  
CORPORATE SOURCE: Dep. Med., Univ. Miami, Miami, FL, 33136, USA  
SOURCE: Oncol. Res. (1993), 5(1), 37-42  
CODEN: ONREE8; ISSN: 0965-0407  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Chronic lymphocytic **leukemia** and lymphoma cells were treated with **antitumor** drugs in vitro and analyzed by flow cytometry to measure the no. of apoptotic (AP) cells and DNA damage in the cells that escaped apoptotic death. AP cells were identified by a high sensitivity of DNA to thermal denaturation, which induced binding of antibody to single-stranded DNA, and by decreased stainability of cells with the intercalating DNA dye propidium iodide. The appearance of AP cells was prevented by Zn++ and inhibited by phorbol ester. AP cells were induced by alkylating agents, **antimetabolites**, and **anthracyclines**. A linear relation between L-phenylalanine mustard dose and the no. of AP cells was obsd. A **synergistic** interaction between drugs was detected by an increased no. of AP cells and by the intensity of DNA damage in non-apoptotic cells. A most interesting example of synergism was the combination of alkylating agents with fludarabine. Linearity of dose-response curves, and the capability to detect drug synergism and to evaluate variable response of cells from different patients to single agents and combinations suggest that flow cytometry of apoptosis will provide a basis for chemosensitivity tests in **leukemia** and lymphoma.

L21 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1989:88615 HCAPLUS  
DOCUMENT NUMBER: 110:88615  
TITLE: Coadministration of glutathione with **antineoplastics** for decreased toxicity and side effects and increased **antineoplastic** efficiency  
INVENTOR(S): Tognella, Sergio; Tedeschi, Michele; Assereto, Roberto  
PATENT ASSIGNEE(S): Boehringer Biochemia Robin S.p.A., Italy  
SOURCE: Eur. Pat. Appl., 13 pp.  
CODEN: EPXXDW  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 265719	A1	19880504	EP 1987-114558	19871006
EP 265719	B1	19910306		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AU 8779398	A1	19880414	AU 1987-79398	19871006
AU 605512	B2	19910117		
ZA 8707502	A	19880629	ZA 1987-7502	19871006
JP 63246334	A2	19881013	JP 1987-253472	19871006
JP 05038730	B4	19930610		
AT 61226	E	19910315	AT 1987-114558	19871006
CA 1306693	A1	19920825	CA 1987-548699	19871006
ES 2036553	T3	19930601	ES 1987-114558	19871006
PRIORITY APPLN. INFO.:			IT 1986-21925	19861007
			IT 1987-48339	19870901
			EP 1987-114558	19871006

AB **Antitumor synergistic** pharmaceuticals contain 2.5-5 g glutathione (GSH)/dose and an effective amt. of .gtoreq.1 **antitumor** agents selected from Pt complexes, oxazaphosphorines, **anthracyclines**, 5-fluorouracil, and methotrexate for simultaneous, sep., or sequential use in chemotherapy. The GSH promotes the activity of the **antitumor** agent(s) while reducing the side effects. A patient with an advanced and relapsing ovarian **tumor** previously treated with cisplatin was treated with a combination of cisplatin 40 mg/m<sup>2</sup> i.v. daily for 5 days for 5 wk, and GSH 35 mg/mg cisplatin i.v., 30 min before each cisplatin dose. The patient showed an extraordinary clin. response after the first cycle of treatment, with the disappearance of a major peritoneal **carcinomatous** ascites. Although usually the 200 mg/m<sup>2</sup>/wk cisplatin dosage is followed by serious side effects after 2 or 3 wk, this patient did not show any side effects even after 5 wk, and she was still alive after 6 mo of the treatment.

L21 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 1988:124491 HCAPLUS  
 DOCUMENT NUMBER: 108:124491  
 TITLE: **Antitumor** agent containing **anthracyclines** and L-ascorbic acid  
 INVENTOR(S): Veltri, Robert W.  
 PATENT ASSIGNEE(S): American Biotechnology Co., Ltd., USA  
 SOURCE: PCT Int. Appl., 11 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8703481	A1	19870618	WO 1986-US2646	19861205
W: AU, JP				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
AU 8768466	A1	19870630	AU 1987-68466	19861205
EP 249632	A1	19871223	EP 1987-900499	19861205

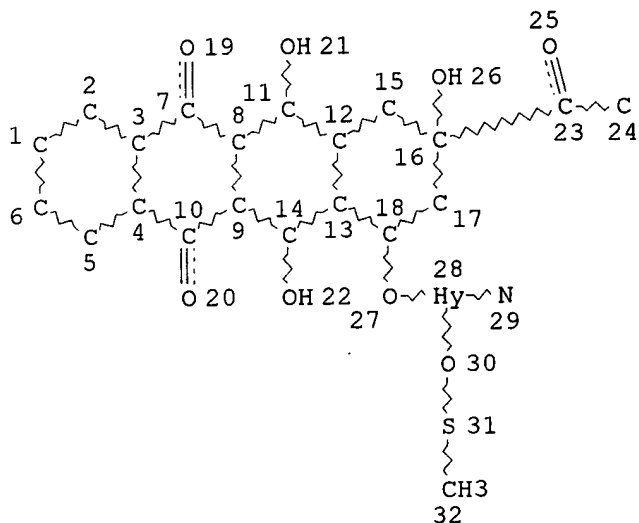


R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE  
 JP 63501722 T2 19880714 JP 1987-500600 19861205  
 PRIORITY APPLN. INFO.: US 1985-804922 19851205  
 US 1986-936770 19861202  
 WO 1986-US2646 19861205

AB An **antitumor** pharmaceutical contains an **anthracycline** Type I **antitumor** agent and L-ascorbic acid (I) in a wt. ratio 20:1-400:1 and in an amt. sufficient to deliver 220-880 mg/kg I and 2-10 mg/kg **anthracycline** type **antitumor** agent, whereby I **synergistically** enhances the activity of the **antitumor** agent. BDF mice suffering from P-388 lymphoma were treated with 5, 10, and 15 mg/kg Doxorubicin, together with 855 mg/kg I and T/C% = 333, 283, and 205, resp. whereas for mice treated with 5, 10, and 15 mg/kg Doxorubicin alone T/C% = 2-5, 144, and 161, resp. For mice treated with 60 mg/kg 5-**Fluorouracil** and 855 mg/kg I, or with 60 mg/kg 5-**Fluorouracil** alone for comparison, the T/C% values were 320, and 170, resp.

=> d stat que

L1 1 SEA FILE=REGISTRY 5-FLUOROPYRIMIDINE/CN  
 L2 16 SEA FILE=REGISTRY (ANTHRACYCLI/BI OR ANTHRACYCLINE/BI)  
 L3 18 SEA FILE=REGISTRY 5-FLUOROURACIL?/CN  
 L4 4 SEA FILE=REGISTRY (GEMCITABINE/CN OR "GEMCITABINE 5'-DIPHOSPHAT E"/CN OR "GEMCITABINE HYDROCHLORIDE"/CN OR "GEMCITABINE TRIPHOSPHATE"/CN)  
 L6 STR



# NODE ATTRIBUTES:

NSPEC IS RC AT 29  
 DEFAULT MLEVEL IS ATOM  
 DEFAULT ECLEVEL IS LIMITED

# GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE

L8 20 SEA FILE=REGISTRY SSS FUL L6  
L9 20578 SEA FILE=REGISTRY CYTIDINE/BI  
L10 21 SEA FILE=HCAPLUS L8  
L11 1093 SEA FILE=HCAPLUS L1 OR FLUOROPYRIMIDI?  
L12 5501 SEA FILE=HCAPLUS L2 OR ANTHRACYCLINE?  
L13 15814 SEA FILE=HCAPLUS L3 OR FLUOROURACIL?  
L14 1223 SEA FILE=HCAPLUS L4 OR GEMCITABINE?  
L15 64733 SEA FILE=HCAPLUS L9 OR CYTIDINE?  
L16 278 SEA FILE=HCAPLUS L12 (L) (ANTIMETABOLITE? OR ANTI(W)METABOLITE?  
OR L15 OR L11 OR L14 OR L13)  
L17 268 SEA FILE=HCAPLUS L16 AND (?CANCER? OR ?CARCIN? OR ?NEOPLAS? OR  
?TUMOR? OR ?TUMOUR? OR ?SARCOM? OR ?LYMPHOM? OR? MELANO? OR  
?LEUKEM? OR ?METAST?)  
L18 3532 SEA FILE=HCAPLUS L12 (L) (?CANCER? OR ?CARCIN? OR ?NEOPLAS? OR  
?TUMOR? OR ?TUMOUR? OR ?SARCOM? OR ?LYMPHOM? OR? MELANO? OR  
?LEUKEM? OR ?METAST?)  
L19 260 SEA FILE=HCAPLUS L17 AND L18  
L20 16 SEA FILE=HCAPLUS L19 AND SYNERGIST?  
L21 16 SEA FILE=HCAPLUS L20 NOT L10  
L22 160 SEA FILE=REGISTRY DAUNORUBICIN  
L23 6411 SEA FILE=HCAPLUS L22 OR DAUNORUBICIN?  
L24 229 SEA FILE=HCAPLUS L23 (L) (ANTIMETABOLITE? OR ANTI(W)METABOLITE?  
OR L15 OR L11 OR L14 OR L13)  
L27 3319 SEA FILE=HCAPLUS L23 (L) (?CANCER? OR ?CARCIN? OR ?NEOPLAS? OR  
?TUMOR? OR ?TUMOUR? OR ?SARCOM? OR ?LYMPHOM? OR? MELANO? OR  
?LEUKEM? OR ?METAST?)  
L28 194 SEA FILE=HCAPLUS L27 AND L24  
L29 13 SEA FILE=HCAPLUS L28 AND SYNERGIST?  
L30 12 SEA FILE=HCAPLUS L29 NOT L21

=> d ibib abs hitrn l30 1-12

L30 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:63809 HCAPLUS

DOCUMENT NUMBER: 134:110448

TITLE: **Synergistic** composition comprising  
**daunorubicin** derivatives and  
**antimetabolite** compounds

INVENTOR(S): Geroni, Maria Cristina; Ripamonti, Marina; Caruso,  
Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia and Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 12 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2001005382 A1 20010125 WO 2000-EP6545 20000710

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,  
CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,  
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,  
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,  
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,  
AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,  
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1200099 A1 20020502 EP 2000-949297 20000710

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL

PRIORITY APPLN. INFO.: GB 1999-16882 A 19990719  
WO 2000-EP6545 W 20000710

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an antimetabolite compd. in the treatment of tumors, esp. in the treatment or prevention of metastasis or in the treatment of tumors by the inhibition of angiogenesis is described. Thus, at a dose of 15 and 60 mg/kg of gemcitabine alone (i.p. day 1 after tumor injection), PNU 159548 alone (i.v. day 1 after tumor injection, administered 2 after gemcitabine), were assocd., without toxicity, with ILS% values of 50 and 83 and 33 and 67, resp. By combining gemcitabine and PNU 159548 at the same doses and with the same schedule, an increase of activity with ILS% values of 117 and 204 were obsd., indicating a **synergistic** effect as shown by the combination index (CI) of 1.4 and 1.3, resp.

IT 65-46-3D, Cytidine, analogs 675-21-8D, 5-Fluoropyrimidine, analogs 20830-81-3D, Daunorubicin, derivs. 95058-81-4D, Gemcitabine, analogs

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**synergistic** compn. comprising **daunorubicin** derivs. and **antimetabolite** compds.)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:57971 HCAPLUS

DOCUMENT NUMBER: 134:246988

TITLE: Induction of differentiation of acute promyelocytic leukemia cells by a cytidine deaminase-resistant analogue of 1-.beta.-D-arabinofuranosylcytosine, 1-(2-deoxy-2-methylene-.beta.-D-erythro-pentofuranosyl)cytidine

AUTHOR(S): Niitsu, Nozomi; Ishii, Yuki; Matsuda, Akira; Honma, Yoshio

CORPORATE SOURCE: Saitama Cancer Center Research Institute, Saitama, 362-0806, Japan

SOURCE: Cancer Research (2001), 61(1), 178-185  
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Since the establishment of all-trans retinoic acid (ATRA) differentiation therapy, the prognosis of acute promyelocytic **leukemia** (APL) has improved, and APL has become a curable subtype of acute myelocytic **leukemia**. Complete remission can be achieved with ATRA alone, but disease-free survival is still too short because of relapse. To overcome this drawback, ATRA has been used in combination with chemotherapeutic agents such as 1-.beta.-D-arabinofuranosylcytosine (araC) and **daunorubicin**. However, growth of the APL cell lines NB4 and HT93 is less sensitive to araC than to that of other myeloid **leukemia** cell lines such as HL-60 and U937. ATRA effectively induced granulocytic differentiation of NB4 and HT93 cells, whereas araC did not, even in a high concn. A **cytidine** deaminase-resistant analog of araC, 1-(2-deoxy-2-methylene-.beta.-D-erythro-pentofuranosyl)**cytidine** (DMDC), inhibited the growth of NB4 and HT-93 cells and was also effective on HL-60 and U937 cells. The promyelocytic cell lines were induced to differentiate by DMDC and other **cytidine** deaminase-resistant analogs. Among them, DMDC was the most potent in inducing differentiation and inhibiting the growth of NB4 cells. The ATRA-induced differentiation of NB4 cells was not augmented by araC, whereas combined treatment with ATRA and DMDC had more than additive effects in inducing the differentiation of NB4 cells. Similar results were obsd. in a primary culture of **leukemia** cells that had been freshly isolated from APL patients. These results suggest that DMDC may play a role in the treatment of APL.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2002 ACS

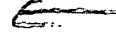
ACCESSION NUMBER: 1985:89762 HCAPLUS

DOCUMENT NUMBER: 102:89762

TITLE: Interaction between human lymphoblastoid interferon and chemotherapeutic agents in vitro

AUTHOR(S): Takahashi, Isao; Oda, Yasuhiro; Lai, Minyu; Fukumoto, Mitsuhiro; Nishimura, Masataka; Yorimitsu, Seiichi; Kitajima, Koichi; Kimura, Ikuro

CORPORATE SOURCE: Med. Sch., Okayama Univ., Okayama, 700, Japan

SOURCE: Acta Med. Okayama (1984), 38(6), 501-4   
CODEN: AMOKAG; ISSN: 0001-6152

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The combined effect of human lymphoblastoid interferon and **anticancer** agents on the growth of MOLT-4 (a human acute lymphocytic **leukemia** cell line) was studied in vitro. The interferon showed a strong **synergistic** interaction in combination with aclarubicin [57576-44-0], cytosine arabinoside [147-94-4] or prednisolone [50-24-8]. It was moderately **synergistic** in combination with adriamycin [23214-92-8] or 5-fluorouracil [51-21-8] and it tended to show additive effects with **daunorubicin** [20830-81-3] or vincristine [57-22-7]. In vitro studies of combination chemotherapy with interferon and **anticancer** agents should yield valuable information as to

the best combination for man.

IT 20830-81-3

RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(**neoplasm**-inhibiting activity of, interferon effect on, in  
human **tumor** cells)

L30 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1984:416965 HCAPLUS

DOCUMENT NUMBER: 101:16965

TITLE: Macromolecular and cell cycle effects of different  
classes of agents inducing the maturation of human  
myeloblastic leukemia (ML-1) cells

AUTHOR(S): Craig, Ruth W.; Frankfurt, Oskar S.; Sakagami,  
Hiroshi; Takeda, Ken; Bloch, Alexander

CORPORATE SOURCE: Grace Cancer Drug Cent., Roswell Park Mem. Inst.,  
Buffalo, NY, 14263, USA

SOURCE: Cancer Res. (1984), 44(6), 2421-9  
CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effect of various classes of differentiation-inducing agents on  
macromol. synthesis was studied in a human myeloblastic **leukemia**  
cell line (ML-1). **Antineoplastic** drugs such as  
1-.beta.-D-arabinofuranosylcytosine [147-94-4],  
**daunorubicin** [20830-81-3], and actinomycin D [50-76-0]  
caused early inhibition of DNA synthesis, which generally preceded the  
accrual of differentiation markers. In contrast, retinoic acid  
[302-79-4] and conditioned medium from mitogen-stimulated leukocytes  
caused a delayed decline in DNA synthesis, which accompanied the  
appearance of maturing morphol. With 12-O-tetradecanoylphorbol-13-acetate  
[16561-29-8], the decline in DNA synthesis was temporally linked to the  
onset of maturation, and this agent evidenced some properties of both the  
**antineoplastic** agents and the more physiol. inducers, retinoic  
acid and conditioned medium. **Antineoplastic** agents and  
conditioned medium, when applied simultaneously, induced differentiation  
in an additive or **synergistic** manner, simulating the effects of  
12-O-tetradecanoylphorbol-13-acetate. RNA and protein synthesis continued  
during maturation induced with all these agents, although a partial redn.  
in RNA synthesis was obsd. at later time points (.gtoreq.24 h). Agents  
incapable of inducing differentiation, such as cordycepin [73-03-0] and  
cycloheximide [66-81-9], were characterized by a lack of sustained  
inhibition of DNA synthesis and/or by early (3 h) inhibition of RNA or  
protein synthesis. The decline in DNA synthesis caused by the inducing  
agents was accompanied by decreased cell cycle progression, cells  
accumulating largely in G1 phase. With **daunorubicin** and  
actinomycin D, block of the G1-S transition was evident at 24 h, whereas  
with conditioned medium and retinoic acid, accumulation in G1 occurred in  
a progressive fashion, >77% of cells residing in this phase on Day 6.  
Maximal inducing doses of 12-O-tetradecanoylphorbol-13-acetate (>80%  
differentiation) caused an accumulation of cells in G1, as well as an  
accumulation of cells with a G2-M-phase DNA content (approx. 40%). These  
observations indicate that early inhibition of DNA synthesis, with sparing  
of RNA and protein synthesis, is characteristic of the

differentiation-inducing **antineoplastic** drugs examd. These agents may induce differentiation by inhibition of the proliferation path, whereas conditioned medium and retinoic acid may act by the stimulation of differentiation paths. Differentiation can be enhanced by the simultaneous application of agents targeting both of these paths.

IT 20830-81-3

RL: PRP (Properties)

(cell cycle and macromol. effects of, in human **leukemia** cells, maturation induction in relation to)

L30 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1981:597080 HCAPLUS

DOCUMENT NUMBER: 95:197080

TITLE: An in vitro model for acute myelogenous leukemia chemotherapy

AUTHOR(S): Koeffler, H. Phillip; Yen, James; Lowe, Leslie

CORPORATE SOURCE: Sch. Med., Univ. California, Los Angeles, CA, USA

SOURCE: Cancer (Philadelphia) (1981), 48(9), 1958-63

CODEN: CANCAR; ISSN: 0008-543X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A human acute myelogenous **leukemia** cell line that forms colonies in soft-gel culture (KG-1) was used to test the effect of various schedules and combinations of chemotherapeutic agents. For comparison, the drug sensitivity of normal human marrow myeloid clonogenic cells was tested. Cytosine arabinoside inhibited both the KG-1 and normal human colony-forming cells (CFC) approx. 25% after a 2-h exposure, 50% after a 5-h exposure, and 90% after a 24-h exposure. **Daunorubicin** had nearly an equal cytotoxic effect on KG-1 and normal marrow CFC after a 2- to 72-h exposure to the drug. **Daunorubicin** at 0.15 .mu.g/mL produced nearly complete inhibition of colony-forming cells. Amphotericin B also inhibited colony formation. Amphotericin B and **daunorubicin**, when combined in culture, produced a **synergistic** suppression of normal and **leukemic** CFC. The **antileukemic** agent 5-azacytidine at a concn. of 0.1 .mu.g/mL produced approx. 60% inhibition of colony formation. **Cytidine** partially rescued CFC when the nucleoside was added in 7-fold excess to cultures contg. 5-azacytidine. **Leukemic** and normal marrow clonogenic cells have nearly the same sensitivity to each chemotherapeutic agent and combination. Human acute myelogenous **leukemia** lines may provide useful models for the development of new chemotherapeutic schedules and combinations.

L30 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1981:473331 HCAPLUS

DOCUMENT NUMBER: 95:73331

TITLE: Potentiation of the action of antitumor agents by hyperthermia

AUTHOR(S): Mizuno, Satoshi; Ishida, Akiko; Amagai, Mihar

CORPORATE SOURCE: Dep. Antibiot., Natl. Inst. Health, Tokyo, 141, Japan

SOURCE: Gan to Kagaku Ryoho (1981), 8(Suppl.), 147-53

CODEN: GTKRDX; ISSN: 0385-0684

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB The effects of several **antitumor** agents in combination with hyperthermia (42.degree. and 43.degree.) on the cell survival of cultured mouse **leukemia** L5178 Y and mammary **carcinoma** FM3 A cells and on the growth of FM3A **tumors** transplanted into the groin of C3H mice were studied. The cytotoxicity of bleomycin [11056-06-7] was markedly increased when the cells were treated with the drug in combination with hyperthermia or were preheated prior to the drug treatment. The combined treatment with bleomycin and microwave heating (42.5.degree., 10 min) inhibited the **tumor** growth **synergistically** with a slight increase in the survival time of mice. The activity of adriamycin [23214-92-8] was also potentiated at elevated temps., but that of daunomycin [20830-81-3] was not. The cellular uptake of 3H-adriamycin into FM3A cells was initially promoted at 43.degree., but was rapidly reduced after 30 min. Any **synergistic** growth delay of FM3A **tumors** was not demonstrated by the combined treatment with adriamycin (2 mg/kg) and hyperthermia. The 2 cell lines were resistant to the cytotoxic action of low concns. of aclacinomycin A [57576-44-0] at 37.degree., but became sensitized at 42.degree. and 43.degree.. The cytotoxicity of macromomycin [12634-34-3] was also greatly increased at 43.degree. and the combined treatment with the drug and hyperthermia inhibited the growth of FM3A **tumors** in vivo **synergistically**. The cytotoxicity of actinomycin D [50-76-0] was also markedly potentiated at 42.degree.. The cytotoxic effects of mitomycin C [50-07-7], neocarzinostatin [9014-02-2], carboquone [24279-91-2], and ACNU [55661-38-6] were also appreciably potentiated at 42.degree. but those of cytosine arabinoside [147-94-4], 5-fluorouracil [51-21-8], and vincristine [57-22-7] were not.

IT 20830-81-3

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(neoplasm inhibition by, hyperthermia effect on)

L30 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1980:579447 HCAPLUS

DOCUMENT NUMBER: 93:179447

TITLE: **Synergistic** cell killing by antitumor agents and hyperthermia in cultured cells

AUTHOR(S): Mizuno, Satoshi; Amagai, Miharuru; Ishida, Akiko

CORPORATE SOURCE: Dep. Antibiotics, Natl. Inst. Health, Tokyo, 141, Japan

SOURCE: Gann (1980), 71(4), 471-8

CODEN: GANNA2; ISSN: 0016-450X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of treatment with several **antitumor** agents in combination with hyperthermia (42.degree. and 43.degree.) on the cell survival of cultured mouse **leukemia** L5178Y and mammary **carcinoma** FM3A cells were studied by following clonal growth in a soft-agar medium. L5178Y cells were more heat-sensitive than FM3A cells. The cytotoxicity of bleomycin [11056-06-7] was markedly increased when the cells were treated with the drug in combination with hyperthermia or were preheated prior to drug treatment. The sensitization of FM3A cells to bleomycin was much more pronounced at 43.degree. than 42.degree.. The

action of adriamycin [23214-92-8] was also potentiated at the elevated temps., but that of daunomycin [20830-81-3] was not. The sensitization of FM3A cells to adriamycin at 43.degree., however, was limited to short times of heat exposure, the cells becoming resistant to further killing by adriamycin after heat exposure times of more than 30 min. The 2 cell lines were resistant to the cytotoxic action of low concns. of aclacinomycin A [57576-44-0] at 37.degree., but they became sensitized at 42.degree. and 43.degree.. The cytotoxicity of actinomycin D [50-76-0] was also markedly potentiated at 42.degree.. The cytotoxic effects of mitomycin C [50-07-7], neocarzinostatin [9014-02-2], carboquone [24279-91-2], and ACNU [55661-38-6] were also appreciably potentiated at 42.degree. but those of cytosine arabinoside [147-94-4], 5-fluorouracil [51-21-8], and vincristine sulfate [2068-78-2] were not.

L30 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1978:609178 HCAPLUS  
DOCUMENT NUMBER: 89:209178  
TITLE: Experimental studies on the cancer treatment with immunopotentiators  
AUTHOR(S): Tsukagoshi, Shigeru  
CORPORATE SOURCE: Cancer Chemother. Cent., Cancer Inst., Japan  
SOURCE: Gan No Rinsho (1978), 24(11), 972-8  
CODEN: GANRAE; ISSN: 0021-4949  
DOCUMENT TYPE: Journal  
LANGUAGE: Japanese

AB Propionibacterium acnes alone, an immunoadjuvant, had no significant effect on P-388 leukemia cells in mice, but P. acnes in combination with mitomycin C [50-07-7], 5-fluorouracil [51-21-8], and daunorubicin [20830-81-3] had synergistic antitumor activity. An immunopotentiating polysaccharide, Krestin (1 g/kg), also showed synergistic effects against P-388 when combined with 1 mg mitomycin C/kg, and this combination was more effective than the combination with either 5-fluorouracil, endoxan [50-18-0], or mercaptopurine [50-44-2]. The optimum time to administer the drugs after immunopotentiators is discussed.

IT 20830-81-3

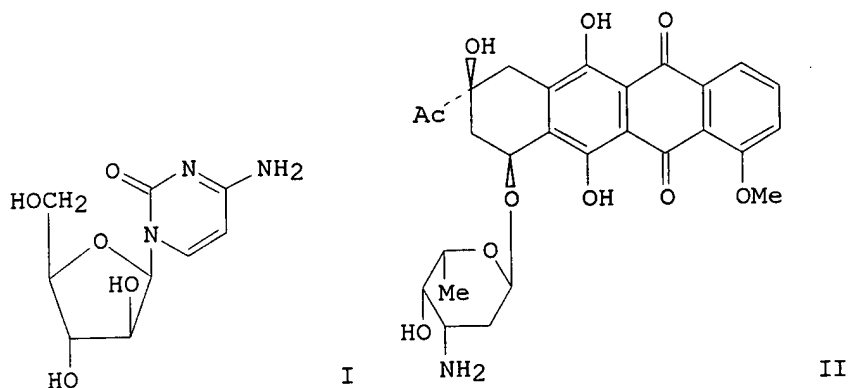
RL: BIOL (Biological study)  
(neoplasm inhibition by immunoadjuvants and)

L30 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1978:484733 HCAPLUS  
DOCUMENT NUMBER: 89:84733  
TITLE: Influence of continuous infusion of cytosine arabinoside on sequencing with daunorubicin in L1210 leukemia  
AUTHOR(S): Edelstein, Mark; Valeriote, Fred; Vietti, Teresa  
CORPORATE SOURCE: Mallinckrodt Inst. Radiol., Washington Univ. Sch. Med., St. Louis, Mo., USA  
SOURCE: Cancer Treat. Rep. (1978), 62(4), 547-8  
CODEN: CTRRDO; ISSN: 0361-5960  
DOCUMENT TYPE: Journal  
LANGUAGE: English



GI



AB A continuous i.v. infusion of cytosine arabinoside (I) [147-94-4] (1 mg) combined with a single i.v. injection of **daunorubicin** (II) [20830-81-3] (0.25 mg) into mice with L1210 leukemia had a cytotoxic effect on **leukemic** cells equal to that predicted for the independent action of the agents. The cytotoxic effects of the 2 agents were less than additive when II was given 12 h before starting I infusion, and the 2 agents were **synergistic** when II was given immediately after I infusion.

IT **20830-81-3**  
RL: BIOL (Biological study)  
(**antitumor** effect of cytosine arabinoside and)

IT **147-94-4**  
RL: BIOL (Biological study)  
(**antitumor** effect of **daunorubicin** and)

L30 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1977:577703 HCAPLUS

DOCUMENT NUMBER: 87:177703

TITLE: Interaction of **antitumor** agents including doxorubicin or **daunorubicin** in **sarcoma**-180 system

AUTHOR(S): Iigo, Masaaki; Kanzawa, Fumihiko; Nakamura, Asako; Hoshi, Akio; Kuretani, Kazuo

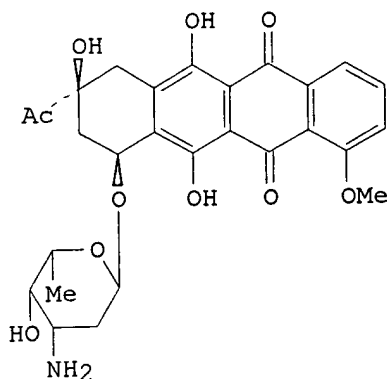
CORPORATE SOURCE: Pharmacol. Div., Natl. Cancer Cent. Res. Inst., Tokyo, Japan

SOURCE: Gann (1977), 68(4), 459-64 CODEN: GANNA2

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB In mice with **sarcoma-180 tumors**, doxorubicin [23214-92-8] was **synergistic** with the following drugs when given on alternate days (ED50 of doxorubicin on days 1, 3, and 5 and the ED50 of the other drug on days 2 and 40): cyclophosphamide [50-18-0], thio-TEPA [52-24-4], carboquone [24279-91-2], actinomycin D [50-76-0], vinblastine [865-21-4], vincristine [57-22-7], methotrexate [59-05-2], cytarabine [147-94-4], 6-mercaptopurine [50-44-2], and L-asparaginase [9015-68-3]. With simultaneous administration (50% of the ED50 of each compd. for 5 days), only cyclophosphamide, carboquone, and cytarabine were **synergistic** with doxorubicin. Upon alternate administration with **daunorubicin (I)** [20830-81-3], the thio-TEPA, mitomycin-C [50-07-7], bleomycin [11056-06-7], actinomycin D, vinblastine, ancytabine [31698-14-3], 6-mercaptopurine, and L-asparaginase showed synergism, whereas upon simultaneous administration with I, cyclophosphamide, thio-TEPA, mitomycin C, bleomycin, actinomycin D, and vinblastine showed synergism. The toxicity of doxorubicin and I in combination with the other drugs was also affected by the schedule of administration. More antagonism of the toxicity was obsd. with simultaneous administration than with alternate administration.

IT 51-21-8 147-94-4 31698-14-3

RL: BIOL (Biological study)

(**daunorubicin** and doxorubicin **antitumor** interaction with)

IT 20830-81-3

RL: BIOL (Biological study)

(**neoplasm** inhibitors synergism with)

L30 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1976:173842 HCAPLUS

DOCUMENT NUMBER: 84:173842

TITLE: Enhanced cytotoxicity in mice of combinations of

concanavalin A and selected antitumor drugs

AUTHOR(S): Bradley, S. G.; Marecki, N. M.; Bond, J. S.; Munson, A. E.; John, D. T.

CORPORATE SOURCE: Virginia Commonw. Univ., Richmond, Va., USA

SOURCE: Adv. Exp. Med. Biol. (1975), 55(Concanavalin A), 291-307

CODEN: AEMBAP

DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Concanavalin A (Con A) [11028-71-0] (50 mg/kg, i.p.) was not lethal for male BALB/c mice. Six hr after administration of 5 mg Con A/kg, the proportion of circulating granulocytes had increased from 23% to 74% of the white cell population; by 24 hr, the proportion of granulocytes had decreased to 56%. Administration of 5 mg Con A/kg 24 hr before 200 mg of 5-[3,3-bis(2-chloroethyl)triazeno]imidazole-4-carboxamide [5034-77-5]/kg, or 100 mg of 5-**fluorouracil** [51-21-8]/kg resulted in a significant enhancement of lethality. Simultaneous administration of 5 mg Con A/kg and 10 mg of daunomycin [20830-81-3]/kg also resulted in enhanced lethality. Administration of 5 mg Con A/kg 24 hr before 40 mg of 1,3-bis(2-chloroethyl)-1-nitrosourea [154-93-8]/kg, 200 mg of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea [13010-47-4]/kg, 1000 mg of cytosine arabinoside [147-94-4]/kg, 0.1 mg of mithramycin [18378-89-7]/kg, 2 mg of pactamycin [23668-11-3]/kg or 1 mg of vincristine [57-22-7]/kg did not result in enhanced lethality. Lipid A prep. from *Escherichia coli* 0127:B8 Boivin lipopolysaccharide was complexed to Con A. The lipid A-Con A complex (5 mg/kg) was no more, or less effective in enhancing the lethality of 5-**fluorouracil** than 2.5 mg Con A/kg. The lipid A-Con A complex (40- mg/kg), given simultaneously with drug, enhanced the lethality for mice given 0.1 mg mithramycin/kg or 1 mg vincristine/kg. In this regard, the lipid A-Con A complex had activity comparable to the complex formed between lipid A and bovine serum albumin. Conceivable, Con A can be used to enhance the susceptibility of **neoplastic** cells to phase-specific **antitumor** drugs, esp. those acting on deoxyribonucleic acid synthesis.

L30 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1975:541934 HCAPLUS

DOCUMENT NUMBER: 83:141934

TITLE: Adriamycin activity in experimental tumors

AUTHOR(S): Goldin, A.; Johnson, R. K.

CORPORATE SOURCE: Div. Cancer Treat., Natl. Cancer Inst., Bethesda, Md., USA

SOURCE: Ergeb. Adriamycin-Ther., Adriamycin-Symp., 2nd (1975), Meeting Date 1974, 3-13. Editor(s): Ghione, M.; Fetzer, J.; Maier, H. Springer: New York, N. Y. ←  
CODEN: 31CHAD

DOCUMENT TYPE: Conference

LANGUAGE: English

GI For diagram(s), see printed CA Issue.

AB The **antitumor** effectiveness of adriamycin (I) [23214-92-8], daunomycin [20830-81-3], rubidazole [54083-22-6], and carminomycin [50935-04-1] against **leukemia** L1210, **leukemia** P388, B16 melanoma, and Lewis lung **carcinoma** was dependent upon the dosage, route, and schedule of administration. The cumulative toxicity of I appeared to be limiting. To this limiting toxicity I was used in combination with other drugs. I was **synergistic** in the treatment of **leukemia** L1210 with a series of **antimetabolites** such as methotrexate [59-05-2] and anhydroara C [31698-14-3], with alkylating agents such as melphalan [148-82-3] and cyclophosphamide [50-18-0], as well as with

miscellaneous agents such as vincristine [57-22-7]. Therapeutic synergism was obsd. both with concomitant and sequential regimens.

IT 20830-81-3

RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(neoplasm inhibition by, adriamycin in relation to)

DOCUMENT TYPE: CODEN: PIXXD2  
 LANGUAGE: Patent  
 FAMILY ACC. NUM. COUNT: English  
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 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050033	A2	20000831	WO 2000-EP746	20000131 <i>check</i>
WO 2000050033	A3	20001221		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1169035	A2	20020109	EP 2000-904990	20000131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008454	A	20020129	BR 2000-8454	20000131
PRIORITY APPLN. INFO.:			GB 1999-4386	A 19990225
			WO 2000-EP746	W 20000131

AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin (I) or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an anti-neoplastic anti-mitotic compd. and/or a platinum deriv. in the treatment of tumors, as well as in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis is disclosed. A dose of 8 mg/kg of oxaliplatin alone (day +3) and a dose of 1 mg/kg I alone (days +1,2) were assocd., without toxicity, with an increase in the lifespan (ILS) values of 83% for both., when the antileukemic activity was detd. in L1210 murine leukemia. Combining oxaliplatin and I at the same doses with the same schedule an increase in the antitumor activity with ILS values of 125% was obsd., indicating a synergistic effect of the combination.

IT **148429-22-5 171047-47-5**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antitumor synergetic combination of daunorubicin deriv. and antimitotic)

L10 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:608574 HCAPLUS

DOCUMENT NUMBER: 133:187946

TITLE: Antitumour synergistic combination of daunorubicin derivative and topoisomerase II inhibitor

INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 13 pp.

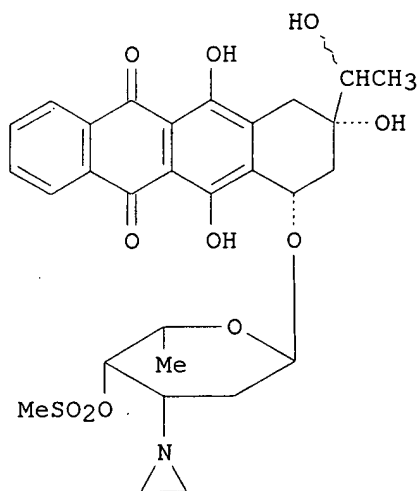
CODEN: PIXXD2

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050032	A1	20000831	WO 2000-EP745	20000131
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1165069	A1	20020102	EP 2000-903657	20000131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008453	A	20020129	BR 2000-8453	20000131
PRIORITY APPLN. INFO.: GB 1999-4387 A 19990225 WO 2000-EP745 W 20000131				
AB The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin (I) or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an antineoplastic topoisomerase II inhibitor in the treatment of tumors and the use of the combination in the treatment or prevention of metastasis or in the treatment of tumors by inhibition of angiogenesis are disclosed. A dose of 13 mg/kg of doxorubicin alone (day +3) and a dose of 1.5 mg/kg I alone (days +1,2) were assocd., without toxicity, with an increase in the lifespan (ILS) values of 50 and 67%, resp. Combining doxorubicin at the same doses with the same schedule an increase in the antitumor activity with ILS values of 150% was obsd., indicating a synergistic effect of the combination.				
IT 148429-22-5 171047-47-5 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (antitumor synergistic combination of daunorubicin deriv. and topoisomerase II inhibitor)				
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT				
L10 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 1999:672833 HCAPLUS DOCUMENT NUMBER: 131:272135 TITLE: Preparation of 13-dihydro-3'-aziridino anthracyclines as anti-tumor agents INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy SOURCE: PCT Int. Appl., 12 pp. CODEN: PIXXD2 DOCUMENT TYPE: Patent				

LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9952921	A1	19991021	WO 1999-EP2567	19990409
W: AU, BG, BR, CA, CN, CZ, HU, ID, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
TW 454012	B	20010911	TW 1999-88104459	19990322
AU 9938174	A1	19991101	AU 1999-38174	19990409
EP 989989	A1	20000405	EP 1999-920684	19990409
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI				
BR 9906305	A	20000620	BR 1999-6305	19990409
JP 2002505691	T2	20020219	JP 1999-551197	19990409
NO 9906127	A	19991210	NO 1999-6127	19991210
US 6258786	B1	20010710	US 1999-445443	19991213
ZA 9907793	A	20000802	ZA 1999-7793	19991221
PRIORITY APPLN. INFO.:			GB 1998-8027	A 19980415
			WO 1999-EP2567	W 19990409
OTHER SOURCE(S):		CASREACT 131:272135		
GI				



I

AB Anthracycline glycosides I (where the wavy line indicates that the 13-hydroxy group may be R, S or a mixt. thereof) are prepd. as anti-tumor agents. The target compds. are prepd. by reducing 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methanesulfonyl daunorubicin with sodium borohydride in an org. solvent at a temp. below 50.degree.C. 13(R/S)-Dihydro-4-demethoxy-

3'-deamino-3'-aziridinyl-4'-methanesulfonyl daunorubicin showed high cytotoxicity (IC50 = 3.76 -20.3 ng/mL) as well as in vivo and in vitro anti-tumor activity against disseminated P388/DX (dose = 2.9-3.8 mg/kg/day).

IT 171047-47-5

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of dihydroaziridino anthracyclines as antitumor agents)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:640094 HCAPLUS

DOCUMENT NUMBER: 131:331689

TITLE: Determination of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulphonyldaunorubicin and its 13-hydroxy metabolite by direct injection of human plasma into a column-switching liquid chromatography system with mass spectrometric detection

AUTHOR(S): Breda, M.; Basileo, G.; Fonte, G.; Long, J.; James, C. A.

CORPORATE SOURCE: Drug Metabolism Research, Pharmacia and Upjohn, Milan, 20014, Italy

SOURCE: Journal of Chromatography, A (1999), 854(1 + 2), 81-92  
CODEN: JCRAEY; ISSN: 0021-9673

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A selective, sensitive, and fully automated column-switching HPLC system using direct injection of human blood plasma followed by MS detection was developed to det. the concns. of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyldaunorubicin (PNU-159548) and its 13-hydroxy metabolite (PNU-169884). A 50-.mu.L human plasma sample was directly introduced into a C4-alkyldiol silica clean-up column sepg. analytes from proteins and polar endogenous compds. using water and methanol as the mobile phase. The fraction contg. PNU-159548 and its metabolite was back-flushed and transferred onto the anal. column. The compds. were sepd. on a Zorbax SB C8 column (150.times.4.6 mm, 5 .mu.m) under gradient elution conditions with the mobile phase of acetonitrile and 2 mM ammonium formate pH 3.5. The MS detection was by atm. pressure ionization with multiple reaction monitoring in pos. ion mode. Linearity was demonstrated over the calibration range of 0.051-10.291 ng/mL for PNU-159548 and 0.104-10.434 ng/mL for PNU-169884. The assay was validated with respect to accuracy, precision, and analyte stability. The method is suitable for use in Phase I clin. studies.

IT 171047-47-5, PNU 159548

RL: ANT (Analyte); ANST (Analytical study)

(detn. of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyldaunorubicin in and its 13-hydroxy metabolite by direct injection of human blood plasma into column-switching HPLC with MS detection)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2002 ACS



ACCESSION NUMBER: 1999:626051 HCAPLUS  
 DOCUMENT NUMBER: 131:252552  
 TITLE: Antitumor composition containing a synergistic combination of an anthracycline derivative with a camptothecin derivative  
 INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino  
 PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy  
 SOURCE: PCT Int. Appl., 14 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9948503	A1	19990930	WO 1999-EP1897	19990319
W: AU, BG, BR, CA, CN, CZ, HU, ID, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2324610	AA	19990930	CA 1999-2324610	19990319
AU 9933314	A1	19991018	AU 1999-33314	19990319
BR 9908391	A	20001031	BR 1999-8391	19990319
EP 1067941	A1	20010117	EP 1999-914528	19990319
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002507571	T2	20020312	JP 2000-537551	19990319
ZA 9902255	A	19991005	ZA 1999-2255	19990323
NO 2000004703	A	20000920	NO 2000-4703	20000920
US 6403563	B1	20020611	US 2000-646096	20000920
PRIORITY APPLN. INFO.: GB 1998-6324 A 19980324 WO 1999-EP1897 W 19990319				
AB There are provided the combined use of 4-demethoxy-3'-deamino-3'-aziridiny-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and an antineoplastic topoisomerase I inhibitor in the treatment of tumors and the use of 4-demethoxy-3'-deamino-3'-aziridiny-4'-methansulfonyl daunorubicin in the treatment of brain tumors.				
IT <b>148429-22-5 171047-47-5</b> RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (anthracycline deriv.-camptothecin compd. antitumor synergistic combination and compn.)				
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT				

L10 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:135051 HCAPLUS  
 DOCUMENT NUMBER: 124:306663  
 TITLE: Sequence-specific DNA interactions by novel alkylating

anthracycline derivatives  
AUTHOR(S): Marchini, S.; Gonzalez, O.; Ripamonti, M.; Geroni, C.;  
Bargiotti, A.; Caruso, M.; Todeschi, S.; D'Incalci,  
M.; Broggin, M.  
CORPORATE SOURCE: Ist. Ricerche Farmacol. Mario Negri, Milan, 20157,  
Italy  
SOURCE: Anti-Cancer Drug Design (1995), 10(8), 641-53  
CODEN: ACDDEA; ISSN: 0266-9536  
PUBLISHER: Oxford University Press  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB New alkylating anthracycline derivs. with promising antitumor activity  
have been synthesized. We selected two of these compds.,  
4-demethoxy-N,N-bis (2 chloroethyl)-4'-methylsulfonyl-daunorubicin (FCE  
27726) and 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyl  
daunorubicin (FCE 28729), comparing their interaction with DNA and that of  
the non-alkylating deriv. 4-demethoxy-4'-methylsulfonyl-daunorubicin (FCE  
27894). The two alkylating derivs. were more cytotoxic than idarubicin  
and presented low cross-resistance with doxorubicin. Both FCE 27726 and  
FCE 28729 were found to alkylate guanines at the N7 position in the major  
groove with roughly the same specificity, but at different concns. FCE  
27726 was 10 times more potent than FCE 28729 in alkylating DNA. At  
higher concns., FCE 27726 was able to alkylate adenines, possibly at the  
N3 position contained in a sequence 5'-PyAA. FCE 27726, as expected, was  
able to form DNA inter-strand cross-links either in vitro and in vivo in  
treated cells. FCE 28729 did not form DNA inter-strand cross-links in  
vivo. In vitro, at high concns., some DNA inter-strand cross-links were  
evident. The non-alkylating deriv. FCE 27894 did not produce any  
alkylation or DNA inter-strand cross-links either in vitro or in vivo.

IT 148429-22-5, FCE 27726 171047-47-5, FCE 28729  
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(alkylating anthracycline; sequence-specific DNA interactions by novel  
alkylating anthracycline derivs. as)

IT 171094-52-3, FCE 27894  
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(non-alkylating anthracycline; sequence-specific DNA interactions by  
novel alkylating anthracycline derivs. as)

L10 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 1995:967133 HCAPLUS  
DOCUMENT NUMBER: 124:9319  
TITLE: Preparation of 4'-O-sulfonylanthracycline derivatives  
as anticancer drugs.  
INVENTOR(S): Bargiotti, Alberto; Caruso, Michele; Grandi, Maria;  
Ripamonti, Marina; Suarato, Antonino  
PATENT ASSIGNEE(S): Pharmacia S.p.A., Italy  
SOURCE: PCT Int. Appl., 15 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9516693	A2	19950622	WO 1994-EP3893	19941124
WO 9516693	A3	19950720		
W: JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 683787	A1	19951129	EP 1995-903277	19941124
EP 683787	B1	19970910		
R: DE, GB, IT				
JP 08506836	T2	19960723	JP 1994-516488	19941124
PRIORITY APPLN. INFO.:			GB 1993-25420	19931213
			WO 1994-EP3893	19941124
OTHER SOURCE(S):		MARPAT 124:9319		
GI				

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Title compds. (I, II; R1 = H, MeO; 1 of R2, R3 = H, the other = R4SO2O; R4 = C1-8 alkyl, aryl which is unsubstituted or substituted with .gtoreq.1 C1-6 alkyl or alkoxy, halo, amino, nitro), were prep'd. Thus, N-trifluoroacetyl-daunorubicin in pyridine was treated with MeSO2Cl at 0.degree. to give 4'-O-methanesulfonyl-N-trifluoroacetyl-daunorubicin. The latter was stirred 6 h with 0.3 N aq. NaOH to give 4'-methanesulfonyl-daunorubicin. 4-Demethoxy-4'-methanesulfonyl-daunorubicin, prep'd. similarly, showed an IC50 = 10.5 ng/mL against LoVo cells, vs. 49.0 ng/mL for doxorubicin.

IT 171094-51-2P 171094-52-3P 171094-53-4P  
171094-56-7P 171333-98-5P 171333-99-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(prepn. of 4'-O-sulfonylanthracycline derivs. as anticancer drugs)

IT 171094-54-5P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of 4'-O-sulfonylanthracycline derivs. as anticancer drugs)

IT 171094-55-6P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of 4'-O-sulfonylanthracycline derivs. as anticancer drugs)

L10 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:960193 HCAPLUS

DOCUMENT NUMBER: 124:9318

TITLE: Preparation of 3'-aziridinoanthracyclines as anticancer drugs.

INVENTOR(S): Bargiotti, Alberto; Caruso, Michele; Grandi, Maria; Ripamonti, Marina; Suarato, Antonio

PATENT ASSIGNEE(S): Pharmacia S.p.A., Italy

SOURCE: PCT Int. Appl., 31 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9516695	A2	19950622	WO 1994-EP3840	19941121 ←
WO 9516695	A3	19950713		
W: AU, BY, CA, CN, FI, HU, JP, KR, KZ, NO, NZ, PL, RU, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2154890	AA	19950622	CA 1994-2154890	19941121
AU 9510660	A1	19950703	AU 1995-10660	19941121
AU 676625	B2	19970313		
EP 683788	A1	19951129	EP 1995-901401	19941121
EP 683788	B1	19970827		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
CN 1117734	A	19960228	CN 1994-191153	19941121
CN 1039123	B	19980715		
HU 73172	A2	19960628	HU 1995-2662	19941121
HU 217630	B	20000328		
US 5532218	A	19960702	US 1994-345450	19941121
AT 157369	E	19970915	AT 1995-901401	19941121
ES 2107294	T3	19971116	ES 1995-901401	19941121
RU 2149163	C1	20000520	RU 1995-120191	19941121
PL 178806	B1	20000630	PL 1994-310177	19941121
IL 111725	A1	19980715	IL 1994-111725	19941122
ZA 9409701	A	19951212	ZA 1994-9701	19941206
FI 9503784	A	19950809	FI 1995-3784	19950809
NO 9503163	A	19951002	NO 1995-3163	19950811
PRIORITY APPLN. INFO.:			GB 1993-25417	A 19931213
			WO 1994-EP3840	W 19941121
OTHER SOURCE(S):		MARPAT 124:9318		
GI				

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Title compds. (I, II; R1 = H, MeO; R2 = H, OH, O2CR5; R5 = C1-8 alkyl, aryl, mono or bicyclic heterocyclyl, each of which may be unsubstituted or substituted with NR6R7, carboxy; R6, R7 = H, alkyl; R3, R4 = H, or 1 of R3, R4 = H and the other = OH or OSO2R8; R8 = alkyl, aryl unsubstituted or substituted by 1-3 substituents which may = alkyl, alkoxy group, halo, nitro), were prepd. Thus, 3'-deamino-3'-(1-aziridinyl)-4'-O-methanesulfonyldoxorubicin, prepd. from 3'-N-(2-chloroethyl)-4'-methanesulfonyldoxorubicin, showed an IC50 = 2.7 ng/mL against LoVo colon adenocarcinoma cells.

IT **171047-46-4P 171047-47-5P 171047-50-0P**  
**171047-52-2P 171047-53-3P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 3'-aziridinoanthracyclines as anticancer drugs)  
IT 171047-58-8 171047-59-9 171047-60-2  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(prepn. of 3'-aziridinoanthracyclines as anticancer drugs)

L10 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:279633 HCAPLUS

DOCUMENT NUMBER: 122:71371

TITLE: Synthesis and study of structure-activity

relationships of new classes of anthracyclines

AUTHOR(S): Suarato, Antonino; Angelucci, Francesco; Bargiotti, Alberto; Caruso, Michele; Faiardi, Daniela; Capolongo, Laura; Geroni, Cristina; Ripamonti, Marina; Grandi, Maria

CORPORATE SOURCE: R&D Oncology-Immunology, Pharmacia-Farmitalia Carlo Erba, Milan, 20159, Italy

SOURCE: ACS Symposium Series (1995), 574 (Anthracycline Antibiotics), 142-55

CODEN: ACSMC8; ISSN: 0097-6156

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Structure-activity studies in the field of anthracyclines have been very fruitful in defining those moieties that are necessary to produce derivs. active on MDR tumor cells. The authors have found that substitutions on the sugar part of anthracyclines are fundamental to confer activity on MDR cells in vitro. In particular, compds. substituted at C-3' of the sugar moiety with 4-morpholino group or selected potential alkylating moieties are able to overcome resistance both in vitro and in vivo.

IT 148429-22-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(structure-activity relationships of new classes of anthracyclines as neoplasm inhibitors)

L10 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:265031 HCAPLUS

DOCUMENT NUMBER: 122:95937

TITLE: Growth-inhibitory properties of novel anthracyclines in human leukemic cell lines expressing either Pgp-MDR or at-MDR

AUTHOR(S): Mariani, Mariangela; Capolongo, Laura; Suarato, Antonino; Bargiotti, Alberto; Mongelli, Nicola; Grandi, Maria; Beck, William T.

CORPORATE SOURCE: Research Center, Pharmacia-Farmitalia Carlo Erba, Milan, Italy

SOURCE: Investigational New Drugs (1994), 12(2), 93-7

CODEN: INNDDK; ISSN: 0167-6997

PUBLISHER: Kluwer

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The objective of the expts. reported in this paper was the identification of promising anthracycline analogs on the basis of lack of

cross-resistance against tumor cells presenting either P-glycoprotein multidrug resistance (Pgp-MDR) or the altered topoisomerase multidrug-resistant (at-MDR) phenotype. Differently modified anthracycline analogs known to be active against MDR cells were assayed in vitro against CEM human leukemic cells, and the sublines CEM/VLB100 and CEM/VM-1 exhibiting resp. the Pgp-MDR and the at-MDR phenotype. Two classes of mols., in which the -NH<sub>2</sub> group in C-3' position is substituted with a morpholino, methoxymorpholino (morpholinyl-anthracycline), or an alkylating moiety, present equiv. efficacy in the drug-sensitive and the two drug-resistant sublines. These results indicate that such mols. may exert their cytotoxic effect through a mode of action different from that of "classical" anthracyclines and is not mediated through topoisomerase II inhibition. Both mols. represent novel concepts in the field of new anthracyclines derivs.

IT 148429-22-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(growth-inhibitory properties of anthracyclines in human leukemic cell lines expressing either P-glycoprotein or altered topoisomerase multidrug resistant phenotype)

L10 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:496068 HCAPLUS

DOCUMENT NUMBER: 119:96068

TITLE: Preparation of alkylamino anthracycline glycosides as antitumors.

INVENTOR(S): Bargiotti, Alberto; Caruso, Michele; Faiardi,

Daniella; Suarato, Antonino; Mongelli, Nicola

PATENT ASSIGNEE(S): Farmitalia Carlo Erba S.r.l., Italy

SOURCE: Eur. Pat. Appl., 13 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

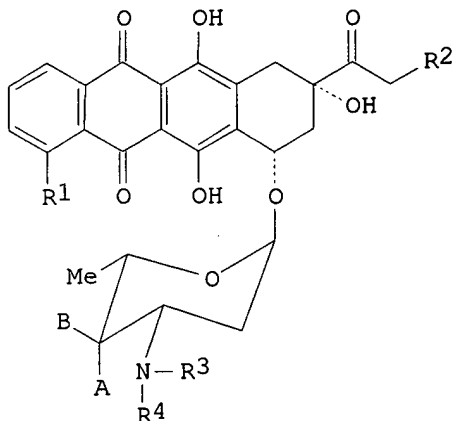
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 521458	A1	19930107	EP 1992-111054	19920630 ←
EP 521458	B1	19960221		
R: AT, BE, DE, DK, FR, GB, GR, IT, NL, PT				
US 5496808	A	19960305	US 1992-904650	19920626
AT 134376	E	19960315	AT 1992-111054	19920630
CA 2112818	AA	19930121	CA 1992-2112818	19920703
WO 9301201	A1	19930121	WO 1992-EP1504	19920703
W: AU, CA, CS, FI, HU, JP, KR, NO, RU				
AU 9222294	A1	19930211	AU 1992-22294	19920703
AU 661012	B2	19950713		
ZA 9204971	A	19930331	ZA 1992-4971	19920703
HU 70480	A2	19951030	HU 1994-22	19920703
HU 218913	B	20001228		
IL 102409	A1	19951208	IL 1992-102409	19920703
RU 2118328	C1	19980827	RU 1994-21658	19920703
JP 3153552	B2	20010409	JP 1993-501958	19920703

CN 1069981	A	19930317	CN 1992-108867	19920704
CN 1031878	B	19960529		
NO 9400026	A	19940216	NO 1994-26	19940104
PRIORITY APPLN. INFO.:			GB 1991-14549	A 19910705
			WO 1992-EP1504	A 19920703
OTHER SOURCE(S):		MARPAT 119:96068		
GI				



AB The title compds. [I; R1 = H, MeO; R2 = H, OH; A, B = H, OH, OSO2R5; R5 = (un)substituted C1-4 alkyl, aryl; R3 = H, (CH2)n-X; R4 = (CH2)n-X; n = 2, 3; X = OH, halo; A = B = H, or one of them = H and the other = OH or OSO2R5; with provisos] and their pharmaceutically acceptable salts are prepd. Daunorubicin was reacted with 3-bromo-1-propanol in DMF at room temp. for 5 days to give 54% I [R1 = MeO, R2 = R3 = H, A = OH, B = H, R4 = (CH2)3OH]. 4-Demethoxy-4'-O-methylsulfonyl-N,N-bis(2-chloroethyl)daunorubicin (also prepd.) had an IC50 of 14.0 ng/mL against human colon adenocarcinoma cells LoVo in vitro vs. 4975 ng/mL for doxorubicin.

IT 148429-22-5P 148429-24-7P 148496-75-7P  
148496-77-9P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(prepn. of, as antitumor)

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DICTIONARY FILE UPDATES: 8 SEP 2002 HIGHEST RN 448182-31-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

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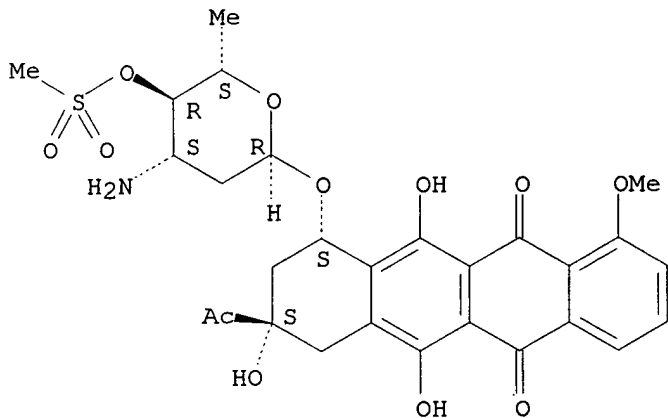
Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> d ide can.l8 1-20

L8 ANSWER 1 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171333-99-6 REGISTRY  
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-amino-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-arabino-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C28 H31 N O12 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

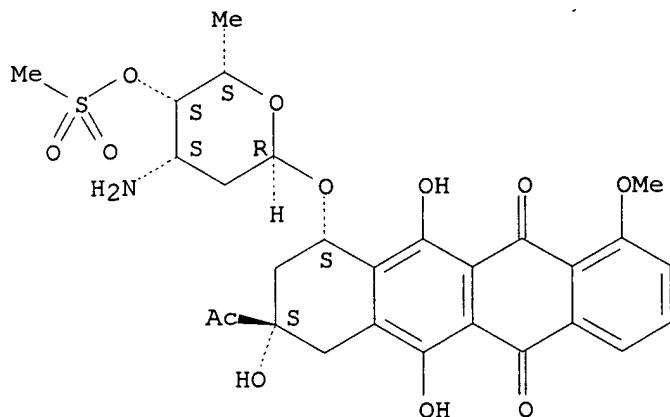
REFERENCE 1: 124:9319

L8 ANSWER 2 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171333-98-5 REGISTRY  
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-amino-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-



6,8,11-trihydroxy-1-methoxy-, (8S-cis)- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C28 H31 N O12 S  
CI COM  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



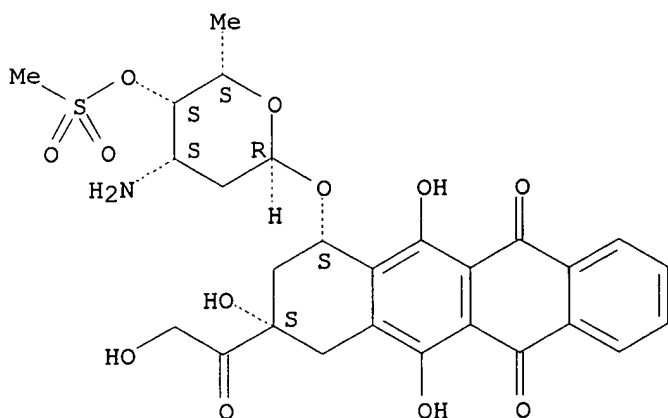
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1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9319

L8 ANSWER 3 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171094-56-7 REGISTRY  
CN 5,12-Naphthacenedione, 7-[[3-amino-2,3,6-trideoxy-4-O-(methylsulfonyl)-  
.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-  
(hydroxyacetyl)-, (7S-cis)- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C27 H29 N O12 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



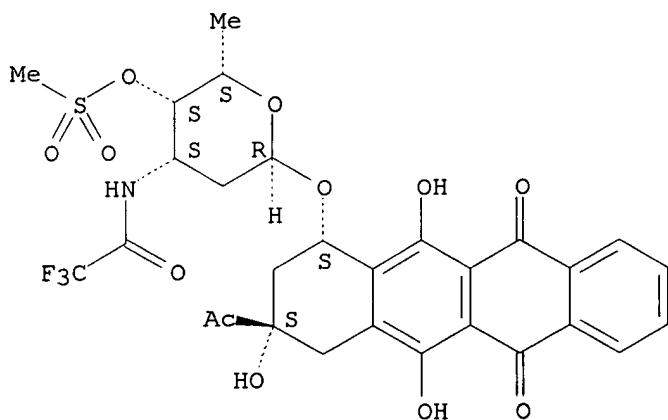
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1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9319

L8 ANSWER 4 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171094-55-6 REGISTRY  
CN 5,12-Naphthacenedione, 9-acetyl-7,8,9,10-tetrahydro-6,9,11-trihydroxy-7-  
[[2,3,6-trideoxy-4-O-(methylsulfonyl)-3-[(trifluoroacetyl)amino]-.alpha.-L-  
lyxo-hexopyranosyl]oxy]-, (7S-cis)- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C29 H28 F3 N O12 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



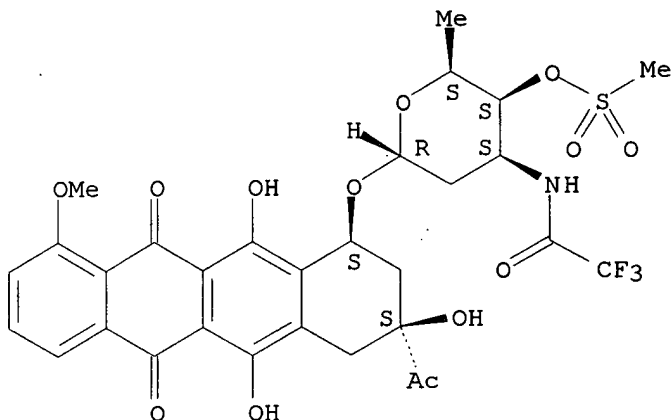
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1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9319

L8 ANSWER 5 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171094-54-5 REGISTRY  
CN 5,12-Naphthacenedione, 8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-4-O-(methylsulfonyl)-3-[(trifluoroacetyl)amino]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S-cis)-(9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C30 H30 F3 N O13 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

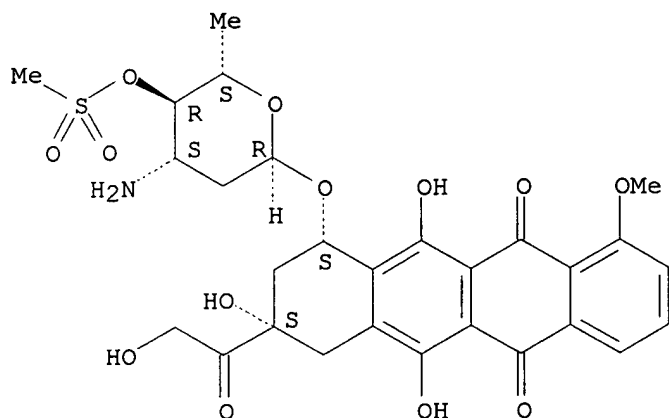
1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9319

L8 ANSWER 6 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171094-53-4 REGISTRY  
CN 5,12-Naphthacenedione, 10-[[3-amino-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S-cis)-(9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C28 H31 N O13 S

SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9319

L8 ANSWER 7 OF 20 REGISTRY COPYRIGHT 2002 ACS

RN 171094-52-3 REGISTRY

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-amino-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S-cis)- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN FCE 27894

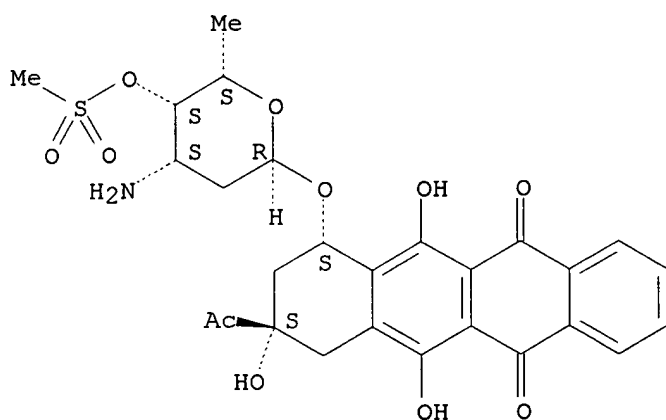
FS STEREOSEARCH

MF C27 H29 N O11 S

SR CA

LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2 REFERENCES IN FILE CA (1967 TO DATE)  
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:306663

REFERENCE 2: 124:9319

L8 ANSWER 8 OF 20 REGISTRY COPYRIGHT 2002 ACS

RN 171094-51-2 REGISTRY

CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-amino-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, hydrochloride, (8S-cis)- (9CI) (CA INDEX NAME)

FS STEREOSEARCH

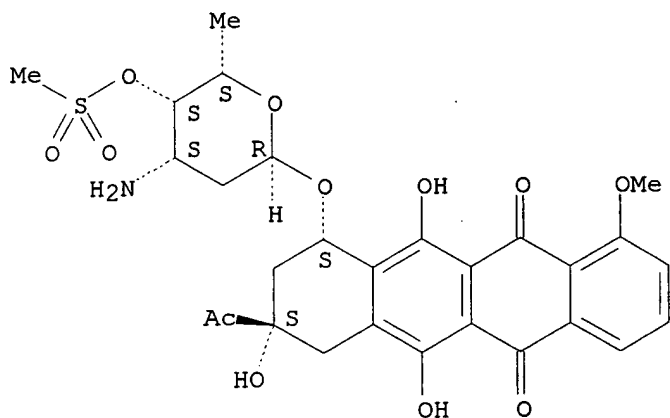
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SR CA

LC STN Files: CA, CAPLUS, TOXCENTER

CRN (171333-98-5)

Absolute stereochemistry.



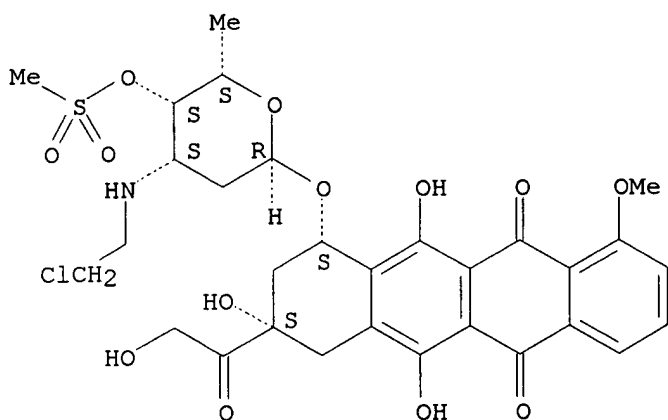
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1 REFERENCES IN FILE CA (1967 TO DATE)  
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REFERENCE 1: 124:9319

L8 ANSWER 9 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171047-60-2 REGISTRY  
CN 5,12-Naphthacenedione, 10-[[3-[(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S-cis)- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C30 H34 Cl N O13 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



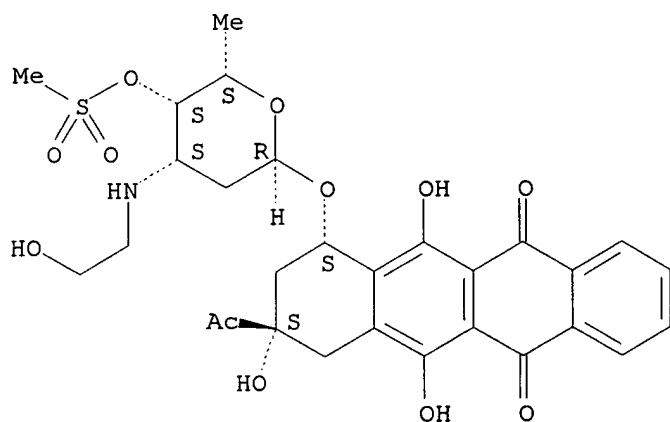
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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9318

L8 ANSWER 10 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171047-59-9 REGISTRY  
CN 5,12-Naphthacenedione, 9-acetyl-7,8,9,10-tetrahydro-6,9,11-trihydroxy-7-  
[[2,3,6-trideoxy-3-[(2-hydroxyethyl)amino]-4-O-(methylsulfonyl)-.alpha.-L-  
lyxo-hexopyranosyl]oxy]-, (7S-cis)- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C29 H33 N O12 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



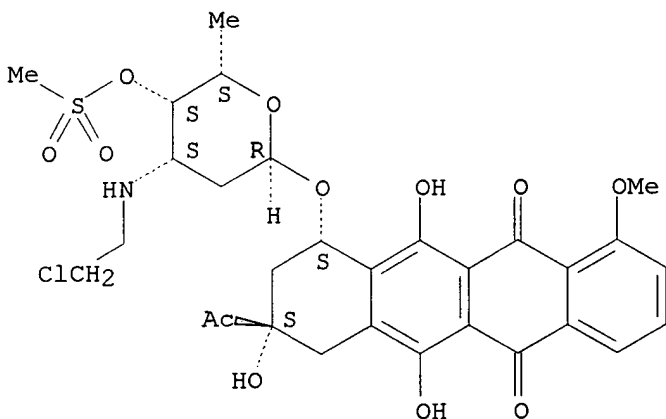
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1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9318

L8 ANSWER 11 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171047-58-8 REGISTRY  
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C30 H34 Cl N O12 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

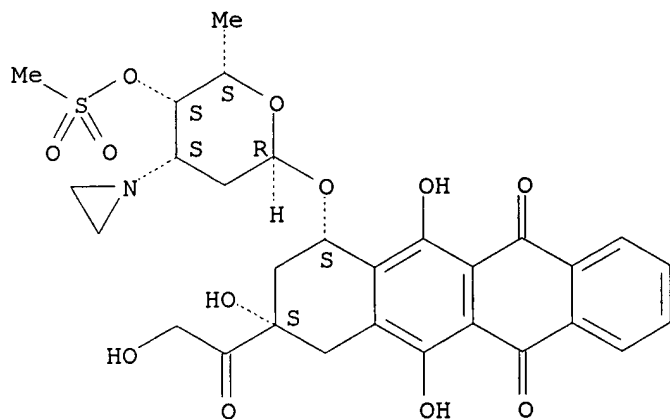
REFERENCE 1: 124:9318

L8 ANSWER 12 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171047-53-3 REGISTRY  
CN 5,12-Naphthacenedione, 7-[[3-(1-aziridiny)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxyacetyl)-, (7S-cis)- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C29 H31 N O12 S  
SR CA



LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



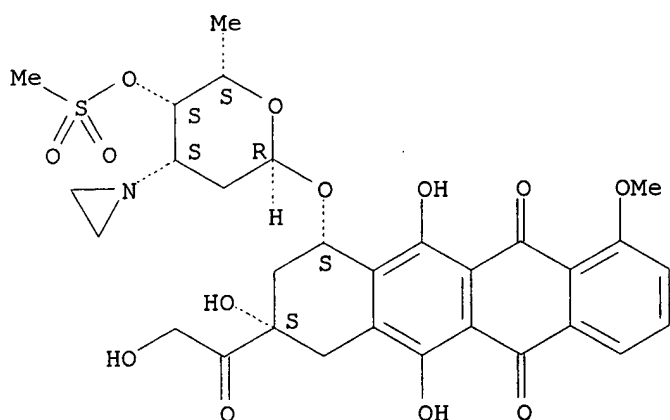
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1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9318

L8 ANSWER 13 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171047-52-2 REGISTRY  
CN 5,12-Naphthacenedione, 10-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S-cis)-(9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C30 H33 N O13 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



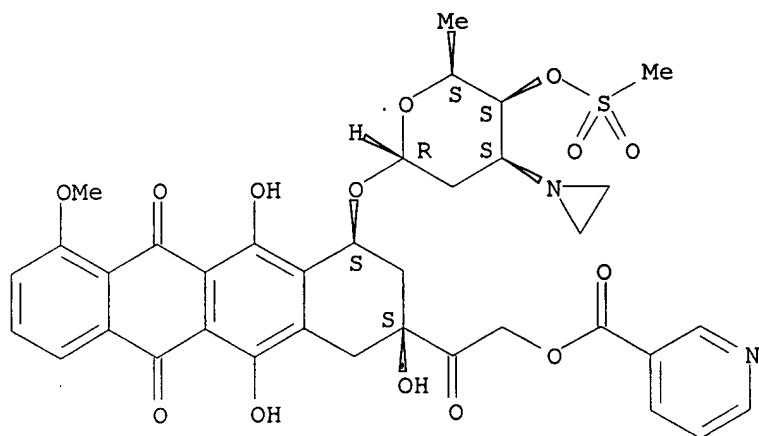
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1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9318

L8 ANSWER 14 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171047-50-0 REGISTRY  
CN 3-Pyridinecarboxylic acid, 2-[4-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]-2-oxoethyl ester, (2S-cis)- (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C36 H36 N2 O14 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9318

L8 ANSWER 15 OF 20 REGISTRY COPYRIGHT 2002 ACS

RN 171047-47-5 REGISTRY

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S-cis)-

OTHER NAMES:

CN FCE 28729

CN Ladirubicin

CN PNU 159548

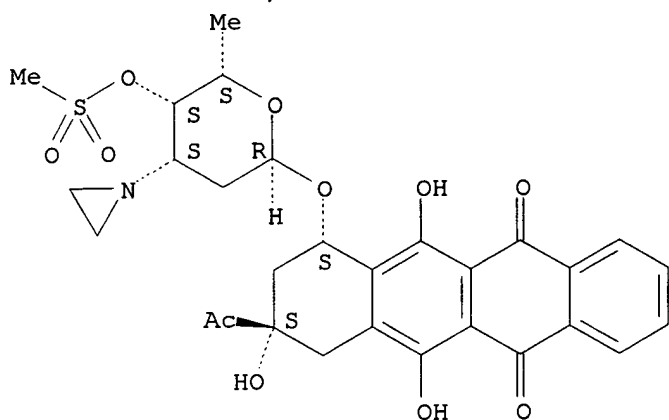
FS STEREOSEARCH

MF C29 H31 N O11 S

SR CA

LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CASREACT, DRUGNL, DRUGUPDATES, PHAR, PROMT, TOXCENTER, USPATFULL

Absolute stereochemistry.

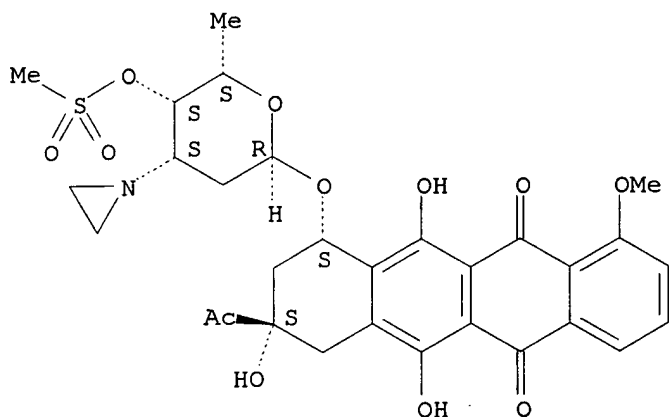


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17 REFERENCES IN FILE CAPLUS (1967 TO DATE)

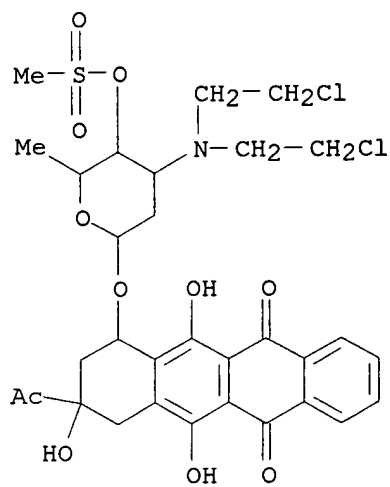
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REFERENCE 6: 134:371802  
REFERENCE 7: 134:242681  
REFERENCE 8: 134:136690  
REFERENCE 9: 134:110448  
REFERENCE 10: 134:508

L8 ANSWER 16 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 171047-46-4 REGISTRY  
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-(1-aziridinyl)-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)-(9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C30 H33 N O12 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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L8 ANSWER 17 OF 20  REGISTRY  COPYRIGHT 2002 ACS
RN 148496-77-9  REGISTRY
CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-
trideoxy-4-O-(methylsulfonyl)-.alpha.-L-arabino-hexopyranosyl]oxy]-
7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S-cis)- (9CI)  (CA INDEX NAME)
MF C31 H35 Cl2 N O11 S
SR CA
LC STN Files:  CA, CAPLUS, TOXCENTER, USPATFULL
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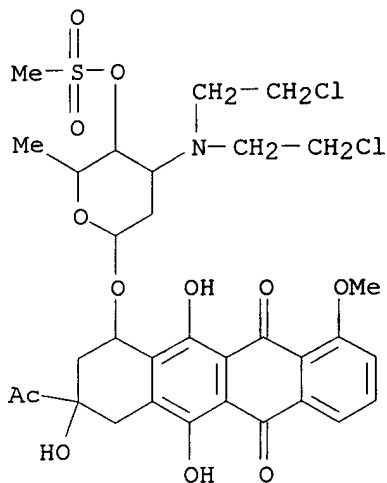


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 119:96068

L8 ANSWER 18 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 148496-75-7 REGISTRY  
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-arabino-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)- (9CI) (CA INDEX NAME)  
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SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

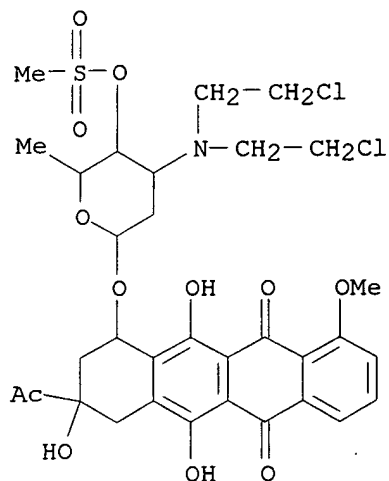


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 119:96068

L8 ANSWER 19 OF 20 REGISTRY COPYRIGHT 2002 ACS  
RN 148429-24-7 REGISTRY  
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)-(9CI) (CA INDEX NAME)  
MF C32 H37 Cl2 N O12 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1967 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 119:96068

L8 ANSWER 20 OF 20 REGISTRY COPYRIGHT 2002 ACS

RN 148429-22-5 REGISTRY

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 5,12-Naphthacenedione, 9-acetyl-7-[[3-[bis(2-chloroethyl)amino]-2,3,6-trideoxy-4-O-(methylsulfonyl)-.alpha.-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S-cis)-

OTHER NAMES:

CN FCE 27726

FS STEREOSEARCH

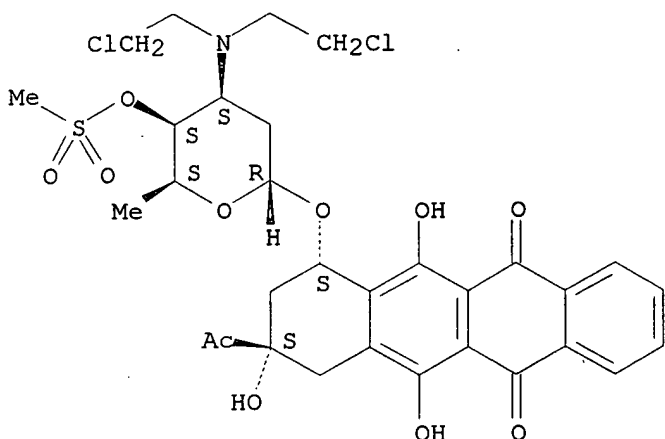
MF C31 H35 Cl2 N O11 S

SR CA

LC STN Files: ADISINSIGHT, CA, CAPLUS, DRUGNL, DRUGUPDATES, PHAR, TOXCENTER, USPATFULL

Absolute stereochemistry.





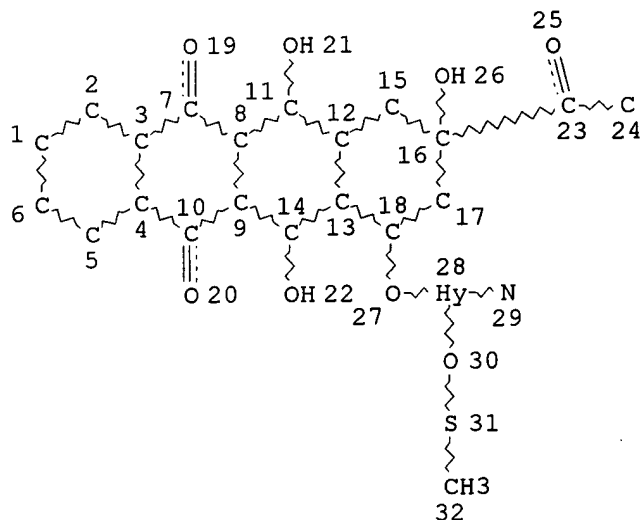
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REFERENCE 4: 133:187946  
REFERENCE 5: 131:252552  
REFERENCE 6: 124:306663  
REFERENCE 7: 122:95937  
REFERENCE 8: 122:71371  
REFERENCE 9: 119:96068

=> d stat que

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L2 16 SEA FILE=REGISTRY (ANTHRACYCLI/BI OR ANTHRACYCLINE/BI)  
L3 18 SEA FILE=REGISTRY 5-FLUOROURACIL?/CN  
L4 4 SEA FILE=REGISTRY (GEMCITABINE/CN OR "GEMCITABINE 5'-DIPHOSPHAT  
E"/CN OR "GEMCITABINE HYDROCHLORIDE"/CN OR "GEMCITABINE  
TRIPHOSPHATE"/CN)  
L6 STR



NODE ATTRIBUTES:

NSPEC IS RC AT 29  
 DEFAULT MLEVEL IS ATOM  
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED  
 NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE

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 L9 20578 SEA FILE=REGISTRY CYTIDINE/BI  
 L10 21 SEA FILE=HCAPLUS L8  
 L11 1093 SEA FILE=HCAPLUS L1 OR FLUOROPYRIMIDI?  
 L12 5501 SEA FILE=HCAPLUS L2 OR ANTHRACYCLINE?  
 L13 15814 SEA FILE=HCAPLUS L3 OR FLUOROURACIL?  
 L14 1223 SEA FILE=HCAPLUS L4 OR GEMCITABINE?  
 L15 64733 SEA FILE=HCAPLUS L9 OR CYTIDINE?  
 L16 278 SEA FILE=HCAPLUS L12 (L) (ANTIMETABOLITE? OR ANTI(W)METABOLITE?  
 OR L15 OR L11 OR L14 OR L13)  
 L17 268 SEA FILE=HCAPLUS L16 AND (?CANCER? OR ?CARCIN? OR ?NEOPLAS? OR  
 ?TUMOR? OR ?TUMOUR? OR ?SARCOM? OR ?LYMPHOM? OR? MELANO? OR  
 ?LEUKEM? OR ?METAST?)  
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 L19 260 SEA FILE=HCAPLUS L17 AND L18  
 L20 16 SEA FILE=HCAPLUS L19 AND SYNERGIST?  
 L21 16 SEA FILE=HCAPLUS L20 NOT L10

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L21 ANSWER 1 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:461733 HCAPLUS  
DOCUMENT NUMBER: 137:72421  
TITLE: Pemetrexed in patients with gastrointestinal  
**carcinoma**  
AUTHOR(S): de Gramont, Aimery; Kindler, Hedy L.  
CORPORATE SOURCE: Hopital Saint-Antoine, Service de Medecine Interne -  
Oncologie, Paris, 75571/12, Fr.  
SOURCE: Seminars in Oncology (2002), 29(2, Suppl. 5), 42-49  
CODEN: SOLGAV; ISSN: 0093-7754  
PUBLISHER: W. B. Saunders Co.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. Gastrointestinal **tumors** are among the most common **cancers** in the world. Palliative chemotherapy is widely used to treat patients with advanced or **metastatic** disease. The mainstay of chemotherapy for colorectal **cancer** is 5-**fluorouracil** (5-FU) modulated by leucovorin (LV), alone or in combination with oxaliplatin or irinotecan (CPT-II). **Gemcitabine** is currently the std. of care in patients with pancreatic **cancer**. There is no std. in gastric **cancer**, although cisplatin, 5-FU, and the **anthracyclines** are the most common drugs used. Pemetrexed, a new-generation antifolate **antimetabolite**, has demonstrated a 15% to 17% response rate in **metastatic** colorectal **cancer**, similar to those of other single agents in previously untreated patients. In patients with advanced pancreatic **cancer**, pemetrexed achieved a 6% response rate and a 28% 1-yr survival rate, which is comparable to single agent **gemcitabine**. Preliminary results in gastric **cancer** are encouraging. The generally mild side effect profile of pemetrexed, esp. with folate supplementation and dexamethasone premedication, and the synergy between pemetrexed and drugs frequently used in gastrointestinal **cancers**, such as irinotecan, oxaliplatin, and **gemcitabine**, suggest that further clin. studies are indicated to det. the role of pemetrexed in the treatment of colorectal, pancreatic, and gastric **cancers**.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:118608 HCAPLUS  
TITLE: Future treatment options with capecitabine in solid  
**tumours**  
AUTHOR(S): Wilke, H.  
CORPORATE SOURCE: Department of Internal Medicine and  
Oncology/Hematology, Kliniken Essen-Mitte, Essen,  
Germany  
SOURCE: European Journal of Cancer (2002), 38(Suppl. 2), *date not*  
S21-S25  
CODEN: EJCAEL; ISSN: 0959-8049  
PUBLISHER: Elsevier Science Ltd.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The oral **fluoropyrimidine**, capecitabine is attracting great interest in the context of **tumor**-selective therapy and

rationally designed combination regimens. Agents such as taxanes upregulate thymidine phosphorylase (TP), and there is therefore a clear rationale for their combination with capecitabine. Preclin. studies of capecitabine/taxane combination therapy demonstrated **synergistic antitumor** activity and phase I studies showed encouraging efficacy. Therefore, a randomised, phase III trial (docetaxel vs. docetaxel/capecitabine) has been initiated in **anthracycline**-refractory **metastatic breast cancer** patients. Recruitment is complete. In colorectal **cancer**, capecitabine/oxaliplatin combination therapy is promising and a phase I, dose-finding trial has been conducted in patients with refractory **metastatic solid tumors**. A similar trial has evaluated capecitabine/irinotecan combination treatment. Capecitabine is also being investigated as adjuvant therapy for colorectal and breast **cancers**. The primary objective of the ongoing X-ACT trial in almost 2000 Dukes' C colon **cancer** patients is to demonstrate at least equiv. disease-free survival between capecitabine and the Mayo Clinic regimen. In addn., the CALGB is planning a randomised, phase III trial of capecitabine vs. doxorubicin/cyclophosphamide or cyclophosphamide/methotrexate/5-**fluorouracil** (CMF) as adjuvant treatment in high-risk, node-neg. breast **cancer** patients aged >65 yr.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:856364 HCAPLUS

DOCUMENT NUMBER: 137:134168

TITLE: Combination chemotherapy of the taxanes and antimetabolites its use and limitations

AUTHOR(S): Smorenburg, C. H.; Sparreboom, A.; Bontenbal, M.; Verweij, J.

CORPORATE SOURCE: Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek), University Hospital Rotterdam, Rotterdam, Neth.

SOURCE: European Journal of Cancer (2001), 37(18), 2310-2323  
CODEN: EJCAEL; ISSN: 0959-8049

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. In an effort to improve response rates of chemotherapy, taxanes were combined with other cytotoxic agents such as **antimetabolites**. However, the use of some of these combinations in patients was restricted by severe toxicity. The significance of the sequence of drug administration in combining methotrexate (MTX) and taxanes was recognized in in vitro studies, showing **synergistic** effects for the sequence of MTX followed by paclitaxel, and antagonism for exposure in the reverse order. A possible explanation might be an MTX-induced synchronization of cells in the S phase of the cell cycle, after which cells are more susceptible for the cytotoxic action of taxanes. Clin. studies using this sequence were hampered by severe neutropenia and mucositis at relatively low doses of both drugs. As no pharmacokinetic interactions were obsd., the excess of toxicity may were due to sequence-dependent **synergistic** actions on bone marrow and

mucosa. In contrast, and confusingly, in vitro studies on 5-fluorouracil (5-FU) and taxanes indicate that 5-FU preceding or simultaneously given to paclitaxel impairs cytotoxicity as compared with paclitaxel monotherapy, while the reverse sequence results in additive or synergistic cytotoxicity. While almost all clin. studies have used the sequence of a taxane followed by 5-FU, various schedules appeared feasible and effective. The combination of a 5-FU analog, capecitabine and taxanes was supported by in vitro data. A large phase III trial confirmed the feasibility and superior efficacy of this combination in breast cancer patients relapsing after an anthracycline. Conflicting results exist on the benefit of combining gemcitabine and taxanes in tumor cell lines. Although the accumulation of gemcitabine triphosphate (dFdCTP) in mononuclear cells was significantly higher with an increasing dose of paclitaxel, no pharmacokinetic interactions for both agents were noticed. A pharmacokinetic anal. of the gemcitabine-docetaxel combination therapy was not published in detail. Despite numerous trials, so far no optimum schedule was established. Regarding data on actually delivered dose intensities, a 2- or 3-weekly cycle seems favorable and feasible. However, possible severe pulmonary toxicity warrants cautious monitoring of patients treated with this combination. Different outcomes of preclin. and clin. studies reveal that combining 2 chemotherapeutic agents is not simply a matter of putting antitumor activities together. Drug interaction may result in synergism, not only of efficacy but also of toxic side-effects. Adding 2 drugs may also implicate antagonism in drug efficacy due to unwanted interference in cytotoxicity or pharmacokinetics. For agents acting at a specific phase of the cell cycle, the sequence of administration may det. the efficacy and toxicity of a combination therapy. Because of an obsd. discrepancy between in vitro data and clin. studies, the authors would like to emphasize the need for adequate dose-finding clin. trials together with pharmacokinetic data anal. before examg. any new combination chemotherapy in more detail in phase II studies.

REFERENCE COUNT: 132 THERE ARE 132 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2001:784864 HCAPLUS  
 DOCUMENT NUMBER: 136:112008  
 TITLE: Vision of the future: Capecitabine  
 AUTHOR(S): Twelves, Chris  
 CORPORATE SOURCE: Cancer Research Campaign Department of Medical Oncology, and Beatson Oncology Centre, University of Glasgow, Glasgow, UK  
 SOURCE: Oncologist (2001), 6(Suppl. 4), 35-39  
 CODEN: OCOLF6; ISSN: 1083-7159  
 PUBLISHER: AlphaMed Press  
 DOCUMENT TYPE: Journal; General Review  
 LANGUAGE: English

AB A review. Capecitabine is a thymidine phosphorylase (TP)-activated oral fluoropyrimidine, rationally designed to generate 5-fluorouracil (5-FU) preferentially within tumors. This tumor selectivity is achieved through exploitation of the

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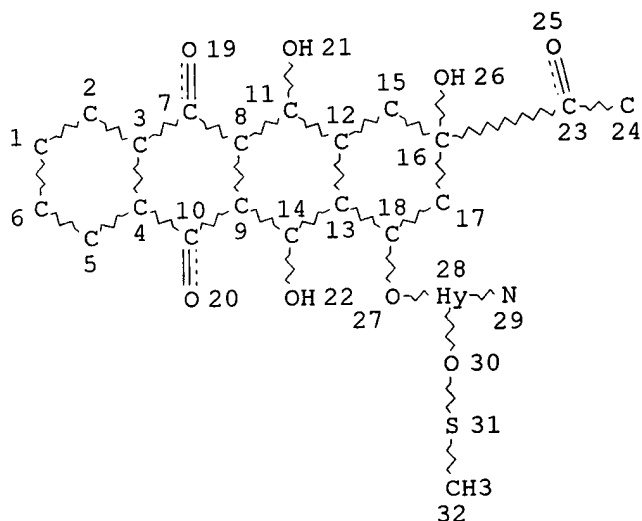
FILE COVERS 1907 - 9 Sep 2002 VOL 137 ISS 11  
FILE LAST UPDATED: 8 Sep 2002 (20020908/ED)

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NODE ATTRIBUTES:  
NSPEC IS RC AT 29  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE  
L8 20 SEA FILE=REGISTRY SSS FUL L6  
L10 21 SEA FILE=HCAPLUS L8

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L10 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2002:220379 HCAPLUS  
DOCUMENT NUMBER: 136:268137  
TITLE: Use of arginine in the preparation of a medicament for  
the prevention and treatment of the side effects  
associated with the intravenous administration of  
pharmaceuticals  
INVENTOR(S): Muggetti, Lorena; Martini, Alessandro; Buzzi,  
Giovanni; Colombo, Paolo  
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy  
SOURCE: PCT Int. Appl., 19 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002022134	A1	20020321	WO 2001-EP10398	20010907
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

AU 2002014974 A5 20020326 AU 2002-14974 20010907  
PRIORITY APPLN. INFO.: IT 2000-MI1984 A 20000912  
WO 2001-EP10398 W 20010907

AB The present invention relates to the use of arginine and, more in particular, to the injectable formulations for i.v. use comprising it, in the prevention and treatment of the side effects assocd. with the extravasation of drugs administered by i.v. route. A salt of estramustine phosphate with arginine was prepd.

IT 171047-47-5, PNU 159548

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(arginine in prepn. of a medicament for prevention and treatment of side effects assocd. with i.v. administration of pharmaceuticals)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS

## RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2001:693333 HCAPLUS  
 DOCUMENT NUMBER: 135:262228  
 TITLE: Crystalline alkycycline derivative  
 INVENTOR(S): Tomasi, Attilio; Ungari, Mario; Galli, Mauro;  
 Fumagalli, Paolo  
 PATENT ASSIGNEE(S): Pharmacia + Upjohn S.p.A., Italy  
 SOURCE: PCT Int. Appl., 13 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

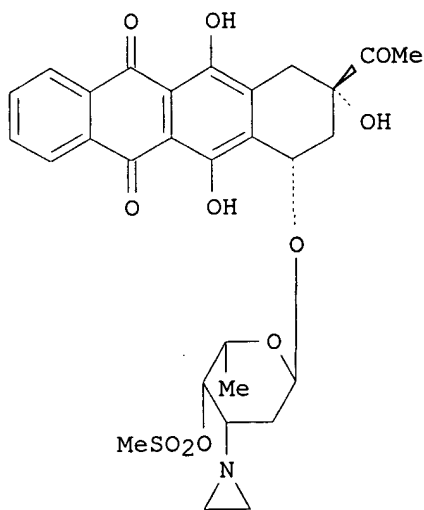
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068661	A2	20010920	WO 2001-EP2783	20010312 <i>check</i>
WO 2001068661	A3	20020321		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
 CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
 HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,  
 LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,  
 SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,  
 YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

GB 2000-6601 A 20000317

GI



I



AB The cryst. form of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (I) is prepd. for use in the prepn. of pharmaceutical compns. for the treatment of tumors. Cryst. I was prepd. from amorphous I using Et acetate and THF for crystn.

IT **171047-47-5**  
 RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (cryst. alkycycline deriv.)

L10 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2001:380379 HCAPLUS  
 DOCUMENT NUMBER: 134:371802  
 TITLE: Lipid complex of alkycyclines as antitumor agents  
 INVENTOR(S): Cherian, Mathew; Bianchi Carnevale, Claudia; Colajori, Elena; Valota, Olga  
 PATENT ASSIGNEE(S): Pharmacia + Upjohn S.p.A., Italy  
 SOURCE: PCT Int. Appl., 17 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001035937	A2	20010525	WO 2000-EP10997	20001030
WO 2001035937	A3	20011220		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1227795	A2	20020807	EP 2000-979540	20001030
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
PRIORITY APPLN. INFO.:			GB 1999-26843	A 19991112
			WO 2000-EP10997	W 20001030

AB An antitumor pharmaceutical compn. comprising a liophilizate of a water insol. alkycycline, a phospholipid, a buffer and a pharmaceutically acceptable lyophilization excipient. The compn. is highly stable and exerts a strong antitumor activity without substantially inducing side effects. Thus, 5 g of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin was dissolved in 100 mL of methylene chloride. To this soln. was added 95g of dimyristoylphosphatidyl choline, 30 g of dimyristoylphosphatidyl glycerol, and 40 g of cholesterol dissolved in 1.7 L of methylene chloride and stirred. To the above soln. was added 4.61 g of phosphate buffer at a pH = 8.5. The two-phase system was stirred using a lab. stirrer and then sparged with nitrogen till the level of methylene

chloride was less than 1%. To this soln. was added a soln. of mannitol and the suspension was then homogenized and freeze dried. The freeze-dried product was stable after 18 mo of storage at -20.degree. and +5.degree., and the product still had over 90% of its initial potency. Efficacy of the compn. in the treatment of patients with solid tumors was shown.

IT 171047-47-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(lipid complex of alkylcyclines as antitumor agents)

L10 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:324240 HCAPLUS

DOCUMENT NUMBER: 136:144749

TITLE: PNU-159548, a novel cytotoxic antitumor agent with a low cardiotoxic potential

AUTHOR(S): Della Torre, Paola; Podesta, Arturo; Imondi, Anthony R.; Moneta, Donatella; Sammartini, Umberto; Arrigoni, Claudio; Terron, Andrea; Brughera, Marco

CORPORATE SOURCE: Worldwide Toxicology, Pharmacia and Upjohn, Milan, Nerviano, 20014, Italy

SOURCE: Cancer Chemotherapy and Pharmacology (2001), 47(4), 355-360

CODEN: CCPHDZ; ISSN: 0344-5704

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purpose: PNU-159548 (4-demethoxy-3'-deamino-3'aziridinyl-4'-methylsulfonyl-daunorubicin), a deriv. of the anticancer idarubicin, has a broad spectrum of antitumoral activity in vitro and in vivo attributable to its DNA intercalating and alkylating properties. The present study was conducted to det. the cardiotoxic activity of PNU-159548 relative to doxorubicin in a chronic rat model sensitive to anthracycline-induced cardiomyopathy. Methods: Young adult male rats were allocated to the following treatment groups: group 1, PNU-159548 vehicle control (colloidal dispersion); group 2, doxorubicin control (saline); groups 3, 4, 5, 6, and 7, PNU-159548 at 0.12, 0.25, 0.50, 0.75, and 1.0 mg/kg, resp.; and group 8, 1.0 mg/kg doxorubicin. Treatments were administered i.v. once weekly for 4 wk (first sacrifice time) or for 7 wk (rats killed at weeks 8, 12, 22, 27, or 35). Body wts., organ wts., serum chem., hematol., serum troponin-T, and cardiac histopathol. were followed throughout the study. Results: Doxorubicin caused irreversible cardiomyopathy evident at week 4 in some rats and progressing in severity in all rats by week 8. There were also marked myelotoxicity, increased liver and kidney wts., testicular atrophy, and about 20% mortality by week 27 in doxorubicin-treated rats. The deaths were attributed to cardiomyopathy and/or nephropathy. PNU-159548 caused a dose-dependent myelotoxicity, with the dose of 0.5 mg/kg per wk being equimyelotoxic to 1.0 mg/kg per wk doxorubicin. PNU-159548 also caused an increase in liver wt. that was reversible and a non-reversible testicular atrophy but, unlike doxorubicin, had no effect on kidney wt. At equimyelotoxic doses, the cardiotoxicity caused by PNU-159548, expressed as the mean total score, was less than one-twentieth of that induced by doxorubicin, and much less than that predicted on the basis of

its content of idarubicin, which is in turn markedly less cardiotoxic than doxorubicin. Conclusions: The novel cytotoxic antitumor deriv., PNU-159548, is significantly less cardiotoxic than doxorubicin at equimyelosuppressive doses. The combination of intercalating and alkylating activities within the same mol. without the cardiotoxic side effects of anthracyclines makes PNU-159548 an excellent candidate for clin. development in oncol.

IT 171047-47-5, PNU-159548

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
(cardiotoxicity of antitumor PNU-159548)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:227312 HCAPLUS

DOCUMENT NUMBER: 135:14016

TITLE: 4-Demethoxy-3'-deamino-3'-aziridinyl-4'-  
methylsulphonyl-daunorubicin (PNU-159548), a novel  
anticancer agent active against tumor cell lines with  
different resistance mechanisms

AUTHOR(S): Marchini, Sergio; Damia, Giovanna; Broggin, Massimo;  
Pennella, Giulia; Ripamonti, Marina; Marsiglio,  
Aurelio; Geroni, Cristina

CORPORATE SOURCE: Lab. Mol. Pharmacol., Istituto di Ricerche  
Farmacologiche "Mario Negri", Milan, 20157, Italy

SOURCE: Cancer Research (2001), 61(5), 1991-1995  
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The activity of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyl-  
daunorubicin (PNU-159548), a new alkylating agent with high antitumor activity  
against a broad range of cancer cells, was evaluated in vitro and in vivo  
in cells selected for resistance to different anticancer agents. Both in  
vitro and in vivo, PNU-159548 did retain its activity in cells expressing  
the multidrug resistance (MDR) phenotype, assocd. to MDR-1 gene  
overexpression or with an alteration in the topoisomerase II gene (altered  
MDR), independently on the drug used for the selection of the resistant  
cell line. According to these data, the intracellular uptake of  
PNU-159548 is not influenced by the presence of MDR-1. PNU-159548 was  
also active, both in vitro and in vivo, against cells showing resistance  
to various alkylating agents (including cisplatin, cyclophosphamide, and  
melphalan) and topoisomerase I-inhibitors. Cells defective in nucleotide  
excision repair, which did show hypersensitivity to treatment with UV  
irradn. and alkylating agents, showed only a marginally increased  
sensitivity to PNU-159548. Similarly, the activity of the drug was not  
influenced by the mismatch repair system, as assessed in two different  
cellular systems deficient in hMLH1 expression and in which hMLH1 activity  
was restored by chromosome 3 transfer. The results obtained clearly  
indicate that the new anticancer agent PNU-159548 is able to overcome the  
classical mechanisms of resistance emerging after treatment with the most  
clin. used anticancer agents, and it could represent an alternate choice  
in the treatment of those tumors refractory to conventional therapy.

IT 171047-47-5, PNU-159548

RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(anticancer agent PNU-159548 is active against tumor cell lines with different resistance mechanisms)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:227311 HCAPLUS

DOCUMENT NUMBER: 135:28784

TITLE: Pharmacological and toxicological aspects of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulphonyl-daunorubicin (PNU-159548): a novel antineoplastic agent

AUTHOR(S): Geroni, Cristina; Ripamonti, Marina; Arrigoni, Claudio; Fiorentini, Francesco; Capolongo, Laura; Moneta, Donatella; Marchini, Sergio; Della Torre, Paola; Albanese, Clara; Lamparelli, Maria Grazia; Ciomei, Marina; Rossi, Rosaria; Caruso, Michele

CORPORATE SOURCE: Department of Pharmacology, Pharmacia Corporation, Milan, 20014, Italy

SOURCE: Cancer Research (2001), 61(5), 1983-1990  
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 4-Demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyl-daunorubicin (PNU-159548) belongs to a novel class of antitumor compds. (termed alkylcycloclines) and is currently undergoing Phase II clin. trial. In the present study, the authors investigated the in vitro and in vivo antitumor activity, the pharmacokinetics, and the toxicol. profile of this compd. PNU-159548 showed good cytotoxic activity in murine and human cancer cells growing in vitro, with an av. concn. for 50% growth inhibition of 15.8 ng/mL. The drug showed strong antitumor efficacy in vivo after i.v. and p.o. administration against rapidly proliferating murine leukemias and slowly growing transplantable human xenografts. At nontoxic doses, PNU-159548 produced complete regression and cures in ovarian, breast, and human small cell lung carcinomas. 14 Of 16 models studied, including colon, pancreatic, gastric, and renal carcinomas, astrocytoma and melanoma, were found to be sensitive to PNU-159548. In addn., PNU-159548 was effective against intracranially implanted tumors. Toxicol. studies revealed myelosuppression as the main toxicity in both mice and dogs. The max. tolerated doses, after a single administration, were 2.5 mg/kg of body wt. in mice, 1.6 mg/kg in rats, and 0.3 mg/kg in dogs. In the cyclic studies, the max. tolerated doses were 0.18 mg/kg/day (cumulative dose/cycle: 0.54 mg/kg) in rats and 0.05 mg/kg/day (cumulative dose/cycle: 0.15 mg/kg) in dogs. PNU-159548 showed minimal cardiotoxicity, when compared with doxorubicin in the chronic rat model at a dose level inducing similar myelotoxicity. Animal pharmacokinetics, carried out in mice, rats, and dogs, was characterized by high vols. of distribution, blood plasma clearance of the same order of the hepatic blood flow, and short terminal half-life. These findings support the conclusion that PNU-159548 is an excellent candidate for clin. trials in the treatment of cancer.

IT 171047-47-5, PNU-159548

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(pharmacol. and toxicol. aspects of PNU-159548, a novel antineoplastic agent)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:208110 HCAPLUS

DOCUMENT NUMBER: 134:242681

TITLE: Formulations for parenteral use of estramustine phosphate and amino acids for cancer treatment

INVENTOR(S): Muggetti, Lorena; Colombo, Paolo; Martini, Alessandro; Buzzi, Giovanni

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 24 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019372	A1	20010322	WO 2000-EP8983	20000913
W:				
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BR 2000014071	A	20020521	BR 2000-14071	20000913
EP 1214078	A1	20020619	EP 2000-967673	20000913
R:				
AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
NO 2002001302	A	20020424	NO 2002-1302	20020315
PRIORITY APPLN. INFO.:			GB 1999-21960	A 19990916
			WO 2000-EP8983	W 20000913

AB A parenteral formulation for cancer treatment comprises estramustine phosphate, a basic amino acid, and a parenterally acceptable carrier or diluent. The formulation can be administered according to a combined chemotherapy regimen in assocn. with one or more chemotherapeutic agents. The formulation enables the estramustine phosphate to be administered with no side effects at the site of injection. Prepn. of estramustine phosphate N-methyl-glucamine salt in admixt. with arginine (estramustine phosphate/meglumine/arginine in a molar ratio 1:1:2) was presented.

IT 171047-47-5, PNU 159548

RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

(combined chemotherapy; formulations for parenteral use of estramustine phosphate and basic amino acids for cancer treatment)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:63847 HCAPLUS

DOCUMENT NUMBER: 134:136690

TITLE: Combination daunorubicin derivative and recombinant human anti-HER2 antibody antitumor agents

INVENTOR(S): Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino

PATENT ASSIGNEE(S): Pharmacia and Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 9 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005425	A2	20010125	WO 2000-EP6540	20000710
WO 2001005425	A3	20010517		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1200098	A2	20020502	EP 2000-945903	20000710
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

PRIORITY APPLN. INFO.: GB 1999-17012 A 19990720  
WO 2000-EP6540 W 20000710

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The combined use of I or II and a recombinant humanized anti-HER2 antibody, preferably trastuzumab, in the treatment of tumors and the use of said combination in the treatment and/or prevention of tumor metastasis is provided.

IT 148429-22-5 171047-47-5

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(combination daunorubicin deriv. and recombinant human anti-HER2 antibody antitumor agents)

L10 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2001:63809 HCAPLUS  
 DOCUMENT NUMBER: 134:110448  
 TITLE: Synergistic composition comprising daunorubicin derivatives and antimetabolite compounds  
 INVENTOR(S): Geroni, Maria Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino  
 PATENT ASSIGNEE(S): Pharmacia and Upjohn S.p.A., Italy  
 SOURCE: PCT Int. Appl., 12 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English *instant*  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005382	A1	20010125	WO 2000-EP6545	20000710 <i>check</i>
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1200099	A1	20020502	EP 2000-949297	20000710
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			
PRIORITY APPLN. INFO.:			GB 1999-16882	A 19990719
			WO 2000-EP6545	W 20000710
AB	The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyldaunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyldaunorubicin and an antimetabolite compd. in the treatment of tumors, esp. in the treatment or prevention of metastasis or in the treatment of tumors by the inhibition of angiogenesis is described. Thus, at a dose of 15 and 60 mg/kg of gemcitabine alone (i.p. day 1 after tumor injection), PNU 159548 alone (i.v. day 1 after tumor injection, administered 2 after gemcitabine), were assocd., without toxicity, with ILS% values of 50 and 83 and 33 and 67, resp. By combining gemcitabine and PNU 159548 at the same doses and with the same schedule, an increase of activity with ILS% values of 117 and 204 were obsd., indicating a synergistic effect as shown by the combination index (CI) of 1.4 and 1.3, resp.			
IT	148429-22-5 171047-47-5, PNU 159548 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (synergistic compn. comprising daunorubicin derivs. and antimetabolite compds.)			
REFERENCE COUNT:	6	THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT		

L10 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2000:824131 HCAPLUS  
 DOCUMENT NUMBER: 134:508  
 TITLE: Combined method of treatment comprising an aromatase inhibitor and a further biologically active compound  
 Di Salle, Enrico; Zaccheo, Tiziana; Tedeschi, Michele  
 INVENTOR(S): Pharmacia & Upjohn S.p.A., Italy  
 PATENT ASSIGNEE(S):  
 SOURCE: PCT Int. Appl., 26 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069467	A1	20001123	WO 2000-EP3407	20000414
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1178831	A1	20020213	EP 2000-917084	20000414
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPLN. INFO.:			GB 1999-11582	A 19990518
			WO 2000-EP3407	W 20000414
AB A compn. for use in breast cancer therapy in humans comprising, in amts. effective to produce a superadditive antitumor effect: (a) an antineoplastic agent in a pharmaceutically acceptable carrier and/or diluent, and (b) an aromatase inhibitor in a pharmaceutically acceptable carrier and/or diluent. The combination of exemestane and epirubicin on DMBA-induced mammary tumors in rats was more effective than either compd. alone.				
IT 171047-47-5, PNU 159548 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (antitumor agent-aromatase inhibitor combinations)				
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT				

L10 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2000:608575 HCAPLUS  
 DOCUMENT NUMBER: 133:187947  
 TITLE: Antitumor synergistic combination of daunorubicin derivative and an antimitotic  
 Geroni, Cristina; Ripamonti, Marina; Caruso, Michele; Suarato, Antonino  
 INVENTOR(S): Pharmacia & Upjohn S.P.A., Italy  
 PATENT ASSIGNEE(S):  
 SOURCE: PCT Int. Appl., 13 pp.